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ASYMMETRIC REDUCTIONS BY CHIRAL LITHIUM-ALUMINUM HYDRIDE AND POTASSIUM-BOROHYDRIDE REAGENTS

EDWARD ROLAND GRANDBOIS

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ASYMMETRIC REDUCTIONS BY CHIRAL LITHIUM-ALUMINUM
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University of New Hampshire

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ASYMMETRIC REDUCTIONS BY CHIRAL
LITHIUM ALUMINUM HYDRIDE
AND
POTASSIUM BOROHYDRIDE REAGENTS

BY

Edward R. Grandbois
B.S., Union College, 1971

DISSERTATION

Submitted to the University of New Hampshire
in Partial Fulfillment of
the Requirements for the Degree of

Doctor of Philosophy
in
Chemistry

September, 1981

This dissertation has been examined and approved.

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TO MY WIFE

TABLE OF CONTENTS

LIST OF TABLES.....	ix
LIST OF FIGURES.....	x
LIST OF ABBREVIATIONS.....	xi
ABSTRACT.....	xii
SECTION	PAGE
I. HISTORICAL.....	1
Introduction.....	1
Alcohol Modified Lithium Aluminum Hydride.....	2
Monohydroxy Alcohols.....	2
Dihydroxy Alcohols.....	7
1,2-Diols.....	7
1,4-Diols.....	13
1,5-Diols.....	16
Amine Modified Lithium Aluminum Hydride.....	17
Monoamines.....	17
Primary Monoamines.....	17
Secondary Monoamines.....	17
Diamines.....	19
Primary Diamines.....	19
Secondary Diamines.....	20
Tertiary Diamines.....	22
Amino Alcohol Modified Lithium Aluminum Hydride.....	23
1,2-Amino Alcohols.....	23
1,3-Amino Alcohols.....	30
Summary and Remarks.....	37

Modified Sodium Borohydride.....	42
II. RESULTS AND DISCUSSION.....	44
Chiral Potassium Borohydride.....	44
Chiral Lithium Aluminum Hydride.....	57
Concluding Remarks.....	78
III. EXPERIMENTAL.....	80
General.....	80
Melting points.....	80
Infrared Spectra.....	80
¹ H Nuclear Magnetic Resonance Spectra.....	80
¹³ C Nuclear Magnetic Resonance Spectra.....	80
Optical Rotations.....	80
Elemental Analyses.....	80
Mass Spectra.....	81
Gas Chromatography Analyses.....	81
Thin Layer Chromatography.....	81
Compounds.....	81
Dry Solvents.....	81
Hydride Reductions.....	81
Analysis of Butyl Lithium Solutions.....	81
Gasometric Analysis of Lithium Aluminum Hydride Solutions.....	82
Analysis of Lithium Aluminum Hydride Solutions by the Stanford Method.....	82
Percent Enantiomeric Excess.....	83
Synthetic.....	83
Ethylene Oxide.....	83
Ethyl (<u>S</u>)-2-(Tetrahydro-2-pyranoxy)propanoate.....	85
(<u>S</u>)-2-(Tetrahydro-2-pyranoxy)-1-propanol.....	85

(S) -1-(p-Toluenesulfonyl)-2-(tetrahydro-2-pyranyloxy)propane.....	86
(S) -1-(p-Toluenesulfonyl)-2-propanol.....	86
(S) -2-Methyloxirane-Method A.....	87
(S) -Propylene Glycol.....	88
(S) -2-Acetoxy-1-bromopropane.....	89
Potassium Pentoxide.....	89
(S) -1,2-Epoxypropane-Method B.....	90
(R) -2-Brosyloxy-1-phenylethanol.....	90
(R) -Styrene Oxide.....	91
(S) -2-(Tetrahydro-2-pyranyloxy)propanamide.....	92
(S) -2-(Tetrahydro-2-pyranyloxy)-1-aminopropane.....	93
Bis[(S) -2-hydroxypropyl]-(S) -2-(tetrahydro-2-pyranyloxy)-1-aminopropane.....	93
Tris[(S) -2-hydroxypropyl]amine-Method A.....	94
Tris[(S) -2-hydroxypropyl]amine-Method B.....	94
Triisopropanolamine Borate.....	95
Potassium Triisopropanolamine Borate Hydride.....	96
Tris[(S) -2-hydroxypropyl]amine Borate.....	96
Potassium Tris[(S) -2-hydroxypropyl]amine Borate Hydride.....	97
Isopropyl Borate.....	98
Potassium Triisopropoxyborohydride.....	99
N,N-Bis[(S) -2-hydroxypropyl]-1-aminobutane.....	99
N,N-Bis[(S) -2-hydroxypropyl]-1,1-dimethyl-1-aminoethane.....	100
N,N-Bis[(S) -2-hydroxypropyl]-(S) -1-phenyl-1-aminoethane.....	101
N,N-Bis[(S) -2-hydroxypropyl]-(R) -1-phenyl-1-aminoethane.....	101
N,N-Bis[2-hydroxyethyl]-(R) -1-phenyl-1-aminoethane.....	102

N,N-Bis[(<u>R</u>)-2-hydroxy-2-phenylethyl]-1-aminobutane.....	103
Recovery of Used Ligands.....	104
6-Tridecyn-8-ol.....	105
6-Methyl-2-heptyn-4-ol.....	106
<u>Tert</u> -butyl Phenyl Ketone.....	107
6-Methyl-2-heptyn-4-one: The Preparation of Acetylenic Ketones.....	108
1-Octyn-3-one.....	109
6-Tridecyn-8-one.....	109
Hydride Reductions.....	110
Reduction of 2-Methylcyclohexanone with Potassium Triisopropanolamine Borate Hydride.....	110
Reduction of 2-Methylcyclohexanone with Potassium Triisopropoxy Borohydride.....	110
Reduction of Propiophenone with (<u>S</u> , <u>S</u> , <u>S</u>)-Potassium Triisopropanolamine Borate Hydride.....	111
Reduction of Ketones with Aminodiol Modified Lithium Aluminum Hydride.....	111
Procedure A.....	111
Procedure B (Mosher's Procedure).....	112
Procedure C (Brinkmeyer's Procedure).....	113
Procedure D (Cohen's Procedure).....	113
Procedure E (Standard Procedure).....	113
Procedure F.....	113
IV. LIST OF REFERENCES.....	114

LIST OF TABLES

1. Reduction of acetophenone by the more efficient modified LAH reagents.....	38
2. Reduction of some phenyl alkyl ketones by the more efficient modified LAH reagents.....	39
3. Some acetylenic ketones reduced with high stereoselectivity by amino alcohol modified LAH.....	41
4. Preliminary reductions with LAH modified by <u>88a</u>	61
5. Reduction of ketones by LAH modified by <u>88a-88d</u>	63
6. Reductions of propiophenone with LAH modified by <u>88b</u>	68
7. Reductions with LAH modified by <u>88d</u>	74

LIST OF FIGURES

1. Redistribution of lithium alkoxyaluminum hydride intermediates.....	3
2. Equilibria producing the chiral reagent when sodium menthoxide is used as an LAH modifier.....	7
3. The preparation of TIPABH.....	45
4. The preparation of (<u>S</u>)-propylene oxide by the Eliel-Furst procedure.....	48
5. The preparation of (<u>S</u>)-propylene oxide via the Golding method.....	50
6. A proposed procedure for the large scale preparation of (<u>S</u>)-propylene oxide.....	51
7. The preparation of (<u>S,S,S</u>)-TIPA via method A.....	52
8. The proposed preparation of (<u>S,R,R</u>)-TIPA.....	54
9. The preparation of (<u>S,S,S</u>)-TIPA via method B.....	54
10. The preparation of (<u>S,S,S</u>)-TIPABH.....	56
11. The preparation of chiral aminodiols.....	59
12. The apparent maximum rotation of PhCH(OH)Et in a mixture of PhCH(OH)Et and PhCOEt, calculated by assuming that the ketone is an inert diluent.....	84

LIST OF ABBREVIATIONS

DME	dimethoxyethane
ee	enantiomeric excess
KTPBH	potassium triisopropoxyborohydride
LAH	lithium aluminum hydride
MEK	methyl ethyl ketone
NBS	N-bromosuccinimide
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPA	triisopropanolamine
TIPAB	triisopropanolamine borate
TIPABH	potassium triisopropanolamine borate hydride
TMEDA	tetramethylethylenediamine
TsO	p-tosyloxy

ABSTRACT

ASYMMETRIC REDUCTIONS BY CHIRAL LITHIUM ALUMINUM HYDRIDE AND POTASSIUM BOROHYDRIDE REAGENTS

by

Edward R. Grandbois

University of New Hampshire, September, 1981

A chiral aminotriol, tris-[(S)-2-hydroxypropyl]amine (1) was synthesized from ammonia and three equivalents of (S)-propylene oxide. The triol was allowed to condense with boric acid to form a bicyclic borate [(S,S,S)-triisopropanolamine borate, 2] which was allowed to react with a suspension of potassium hydride in tetrahydrofuran to form a borate hydride [potassium (S,S,S)-triisopropanolamine borate hydride, 3]. Propiophenone was reduced to optically active alcohol in 14% enantiomeric excess (ee) (R) by 3 in THF.

By reaction of n-butylamine, t-butylamine and (R)- and (S)-1-phenylethylamine with two equivalents of (S)-propylene oxide or ethylene oxide five chiral aminodiols were prepared: N-n-butyl-bis-[(S)-2-hydroxypropyl]-amine (4), N-[(R)-1-phenylethyl]-bis-(2-hydroxyethyl)amine (5), N-[(R)-1-phenylethyl]-bis-[(S)-2-hydroxypropyl]amine (6), N-[(S)-1-phenylethyl]-bis-[(S)-2-hydroxypropyl]amine (7) and N-[tert-butyl]-bis-[(S)-2-hydroxypropyl]amine (8).

The aminodiols were added to ethereal lithium aluminum hydride (LAH) to produce chiral, modified LAH reagents which were used to reduce prochiral ketones. The modified LAH reagents from ligands 4, 5, 6 and 7

quantitatively reduced acetophenone [44%ee(R), 10%ee(S), 35%ee(R) and 82%ee(R), respectively] and propiophenone [57%ee(R), 10%ee(S), 19%ee(R) and 77%ee(R), respectively]. A general additivity of asymmetric induction due to the chiral centers in the carbinol and noncarbinol arms of the ligands was perceived, with 7 optimizing the inductive influences. The direction of the asymmetric induction was rationalized by means of a stereocorrelation model in which the ketone is coordinated with a lithium cation that is simultaneously coordinated with the nitrogen and two oxygens of the aminodiol ligand (in the form of a dialkoxydihydroaluminumate).

Unique and unpredictable behavior was observed with the LAH reagent from 8. The enantiomeric composition was observed to vary wildly [83%ee(R) to 32%ee(S)] in roughly comparable reductions of propiophenone. This strange behavior has not been fully rationalized.

I. HISTORICAL

Introduction

As the demand for more economical and efficient routes to natural products, pharmaceuticals and many other chiral organic compounds has increased, asymmetric synthesis has acquired a more prominent position and is the subject of intensive current research. Asymmetric synthesis has been defined as "a reaction in which an achiral unit in an ensemble of substrate molecules is converted by a reactant into a chiral unit in such a manner that the stereoisomeric products are produced in unequal amounts."¹ Of the methods available for obtaining optically active materials, asymmetric synthesis is attractive because theoretically it allows all of a prochiral substrate to be converted to a desired optical isomer. This is in contrast, for example, to classical resolution or kinetic resolution where the maximum yield is 50% of a desired isomer. Thus, in terms of the efficiency of conversion of intermediates to desired product an asymmetric synthesis is a superior strategy.

The different approaches utilized in asymmetric synthesis have been extensively reviewed.¹⁻⁷ One of the most frequently studied asymmetric reactions is the reduction of ketones to optically active 2° alcohols.* The most successful and widely used approach to this problem is to use lithium aluminum hydride (LAH) modified by an

*In a much less common variation, deuterium labeled aldehydes or unlabeled aldehydes have been reduced to chiral labeled alcohols by unlabeled or labeled chiral reagents, respectively.

optically active compound as the asymmetric reducing agent.

Alcohol Modified Lithium Aluminum Hydride

Monohydroxy Alcohols

The first report of an asymmetric reduction of ketones appeared in 1951 with Bothner-By's claim⁸ that he had asymmetrically reduced methyl ethyl ketone (MEK) and methyl tert-butyl ketone with LAH partially reacted with d-camphor, 4.^{*} It was later found⁹ that the optical activity of the products of these reductions was due to the presence of small amounts of d-isoborneol. One explanation for the complete lack of asymmetric induction was the possible redistribution of the intermediate chiral alkoxyaluminum hydride causing the actual reducing agent to be LiAlH_4 as, for example, in Figure 1. Cervinka also reported failure in an attempt to asymmetrically reduce ketones with LAH partially decomposed by (-)-menthol, 1, or (+)-borneol 2.¹⁰ There is, however, one report of the successful reduction of an aliphatic ketone by LAH modified by such a monohydroxy alcohol. Minoura reported having reduced MEK to methylethylcarbinol in ca. 2% enantiomeric excess (ee) by using LAH modified by d-camphor, 4.¹¹

Considerably more asymmetric induction was realized when α - and β -dialkylamino ketones were reduced by LAH partially decomposed by 3 equivalents of (-)-menthol, 1. With this reagent Angeloni obtained amino alcohols in 77.5 and 95% ee from the reduction of β -dimethylamino-propiophenone and α -morpholinoacetophenone, 5a, respectively.^{12,13} Generally, ee values increased with decreased reaction temperature

*This is roughly equivalent to modification with (+)-isoborneol since the LAH reduction of camphor gives approximately a 90:10 ratio of isoborneol:borneol.

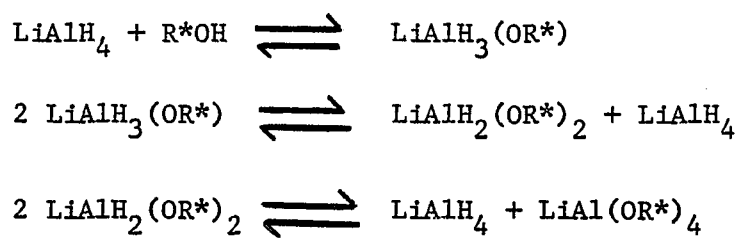
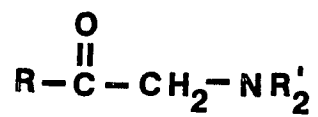


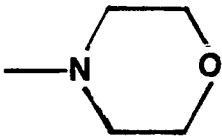
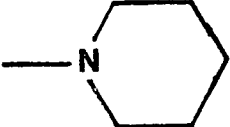
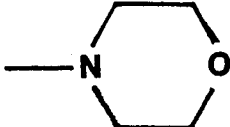
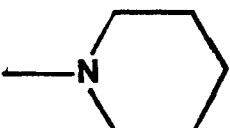
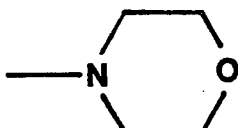
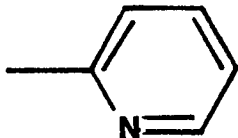
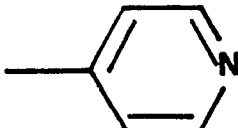
Figure 1. Redistribution of lithium alkoxyaluminum hydride intermediates.

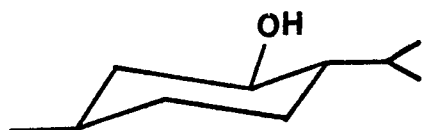
and decreased with increasing bulk of the substituent α to the carbonyl group (Me < Ph < t-Bu). There was a curious reversal in the direction of the asymmetric induction when the reaction temperature was changed from 0 to -78°C in the reduction 5b-5e. No explanation for this phenomenon was offered. The generally high % ees obtained with these substrates and the fact that reduction of 5f resulted in significant asymmetric induction (44% ee) but 5g gave a racemic product suggest that the nitrogen of the ketobase participates in the transition state.

Although Yamaguchi was unable to reproduce some of the high optical yields reported by Angeloni, he was able to specify the function of the amino group. In a study of the reduction of a series of ω -substituted alkyl phenyl ketones ($\text{PhCO}(\text{CH}_2)_n\text{Y}$; $n = 1-4$; $\text{Y} = \text{H}, \text{Me}, \text{Et}, \text{SMe}, \text{OMe}, \text{NMe}_2$) by LAH/3-(-)-menthol it was concluded that the Li cation coordinated with the carbonyl group and the heteroatom (O and N, but not S).¹⁴ Therefore the reduction proceeded via a cyclic transition state the rigidity of which is determined by the size of the ring. It was pointed out, however, that ease of chelate ring formation does not always result in enhanced stereoselectivity.

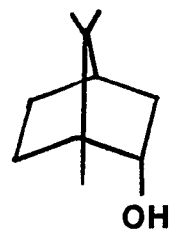
Using LAH modified by (-)-menthol, 1, (+)-borneol, 2, (+)-homofenchylalcohol, 3, and (+)-camphor, 4, Cervinka was able to reduce pyrrolinium salts and ketimines to the corresponding amines of low optical purity.¹⁵⁻¹⁷ Two findings in this study of the reduction of pyrrolinium salts by modified LAH warrant attention. One is the reversal in the stereochemistry of the product when 3 rather than 1 or 2 equivalents of menthol were used.^{15,16} More significant is the finding that the use of 1 equivalent of the sodium alcoholate of menthol

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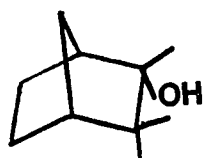
	R	NR' ₂
a	Ph	
b	<u>t</u> -Bu	
c	<u>t</u> -Bu	
d	Me	
e	Me	
f	Me	
g	Me	



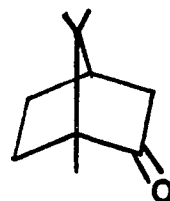
(-)-Menthol, 1



(+)-Borneol, 2



(+)-Homofenchylalcohol, 3



(+)-Camphor, 4

as a modifier resulted in approximately the same asymmetric induction as when menthol itself was used.¹⁵ This was interpreted as suggesting a set of equilibria, are involved in reagent formation, Figure 2.

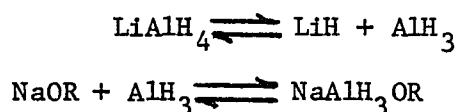


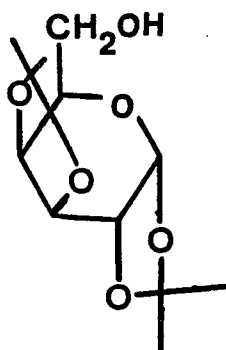
Figure 2. Equilibria producing the chiral reagent when sodium menthoxide is used as an LAH modifier.

Monohydroxy sugar derivatives, 6 and 7, were used by Cervinka as LAH modifiers in ketone reductions with little success.¹⁸ The rotations of the resulting alcohols ranged from 0.18° for phenylmethylcarbinol to 3.8° for phenyl-1-naphthylcarbinol. Low ee values were also obtained when phenylmethyl- and tert-butylmethylcarbinols were used as modifiers in the reduction of ketones.¹⁶ However, as a result of this study it was proposed that better results were obtained when the substrate contained a nitrogen atom. Cervinka believed that a nitrogen atom in either the substrate or the modifier would coordinate with the aluminum resulting in a more rigid transition state and therefore greater asymmetric induction. The lack of such coordination was given as a possible reason for the low ee values in the above mentioned reductions.

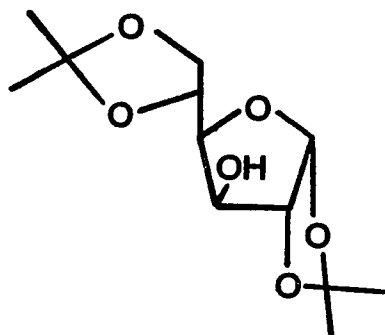
Dihydroxy Alcohols

1,2-Diols

In an effort to eliminate disproportionation of the alkoxy-aluminum hydride, Haller and Schneider used pinanediol as an LAH modifier.^{19,20} Presumably a bidentate ligand would be less susceptible

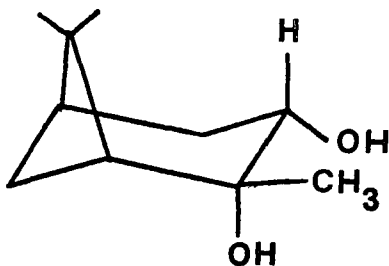


1,2:3,4-Di-O-isopropylidene-
 α -D-galactopyranose, 6

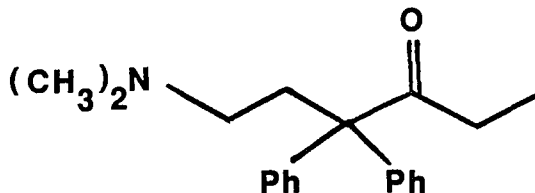


1,2:5,6-Di-O-isopropylidene-
 α -D-glucofuranose, 7

to disproportionation. A series of benzyl alkyl ketones was reduced. Cis-pinanediol, 8, gave higher % ee values than the trans isomer. The best result, 32.8% ee, was obtained when normethadone, 9, was reduced with LAH modified by one equivalent of cis-pinanediol plus one equivalent of benzyl alcohol. Although S alcohols were consistently produced when LAH/8/benzyl alcohol was used as the reducing agent, the direction of the stereoselectivity reversed, S to R, in going from ethyl to n-propyl benzyl ketone when no benzyl alcohol was added.



(1R,2R,3S,5R)-(cis)-Pinanediol, 8

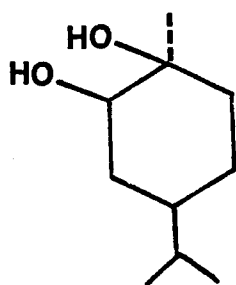


Normethadone, 9

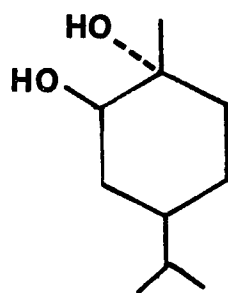
Lund used seven terpenic alcohols, 10-16, as LAH modifiers.²¹ Acetophenone was reduced by these reagents in various solvents and at a variety of temperatures. Enantiomeric excesses of 15% (S) to 30% (R) were obtained. Diol 10 was superior to all others. The best result, 30% ee, was obtained when 1.0 mole of ketone was reduced by the reagent prepared by dropwise addition of an ether solution of 10 (2.0 moles) to LAH (4.6 moles) in ether followed by dropwise addition of ethanol (8.7 moles) to destroy excess hydride.

The results of this study were discussed in some detail and two

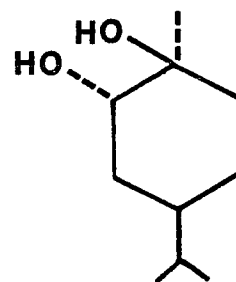
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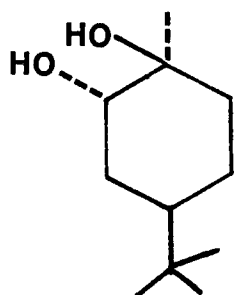
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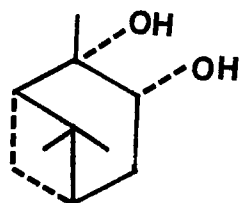
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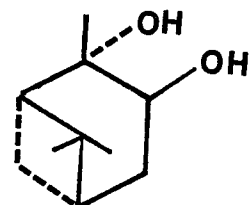
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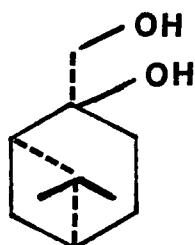
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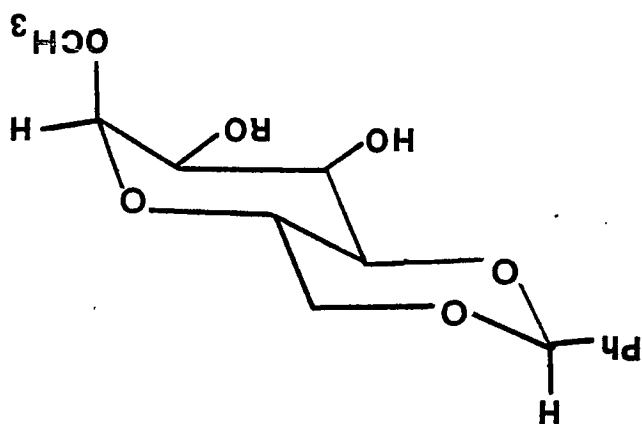
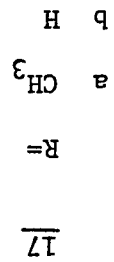
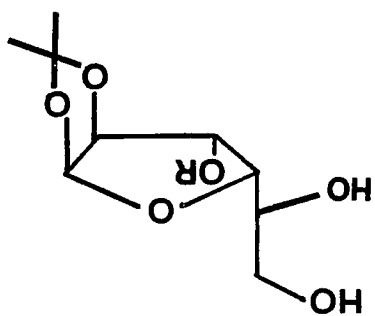
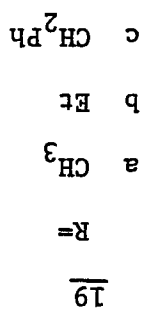
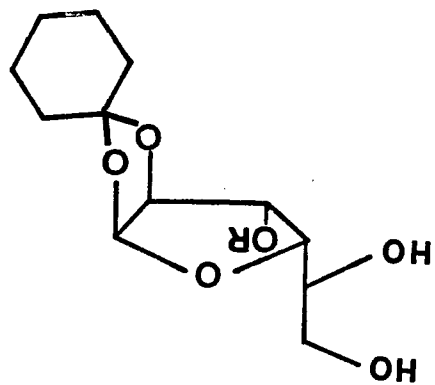
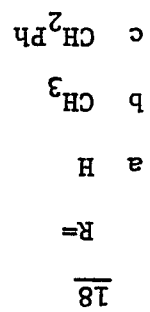


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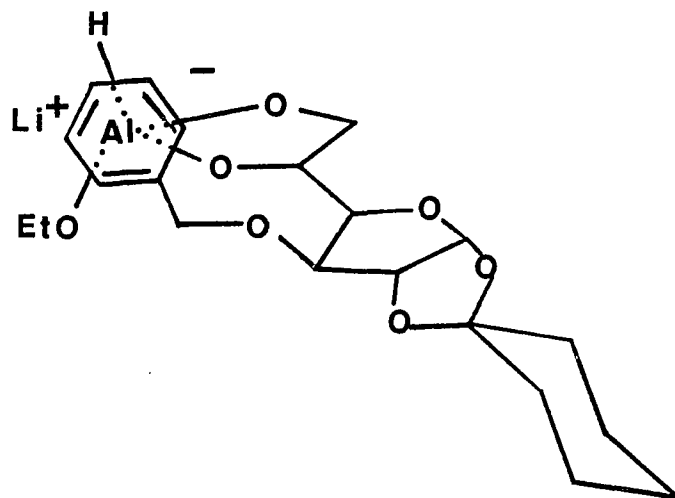
findings deserve mentioning here. The temperature at which the reagent was prepared had a significant effect on the optical yield. Increased disproportionation and incomplete reaction of alcohol with LAH were given as the reason for decreased optical yield at temperatures higher and lower than 20°C, respectively. In a pair of experiments where the reagent was LAH/10/EtOH (1:1:1) in THF, S alcohol resulted when the reduction was run at 25°C and R isomer was produced at 66°C. This was one of the first reports of a stereoselectivity reversal associated with reaction temperature in such reactions.

Landor reported the use of several glucose derivatives, 17-19, as LAH modifiers in the reduction of a variety of substrates.²²⁻²⁹ Low optical yields of less than 15% ee were obtained when LAH modified with 1 equivalent of 17, 18, 19a or 19b, was used to reduce a variety of ketones.^{22,23} Derivative 19c was the superior modifier. Reduction of acetophenone by this reagent afforded the corresponding carbinol in 19.2% optical purity. The optical yield in the reduction of propiophenone was increased to nearly 40% ee by varying the ratio of LAH/19c and by using a standardized LAH solution.²⁴ It is interesting to note that of the 8 complexes derived from these glucose derivatives only that from 19c was significantly soluble in ether.

Up to 70% ee was obtained in the reduction of acetophenone by LAH/19c/EtOH.²⁶ The ratio of ketone/LAH/19c/EtOH (1:4:2:8) merits some discussion. The use of excess LAH presumably insures formation of the cyclic complex. Then unreacted LAH and the more reactive of the two hydrides on the alkoxyaluminum hydride are destroyed leaving the complex shown, 20. Adding more EtOH than necessary resulted in decreased optical yields due to destruction of both hydrides of the



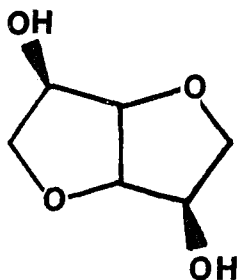
chiral complex and a concomitant increase in reduction by the less reactive, undissolved, unmodified hydride species present in the suspension. The use of a standardized LAH solution instead of solid LAH gave more consistent results. With this method of preparation excess EtOH was not detrimental to the optical yield which would suggest that the undissolved material was indeed affecting the optical yield as described.



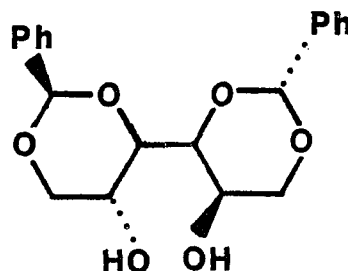
1,4-Diols

One difficulty in interpreting results obtained in reductions by diol modified LAH reagents stems from the inequality of the two hydrides in the complex. In an attempt to clarify this situation, Baggett & Striblehill used mannitol derivatives, 21 and 22, containing a C_2 axis of symmetry to modify LAH.³⁰ Unfortunately, these reagents produced optical yields of less than 15% ee and the stereochemical results could not be correlated with the proposed models. A curious drop in

enantioselectivity was observed when solid 21 instead of a solution of it was added to the LAH solution. This phenomenon was not explained.



1,4:3,6-Dianhydro-D-mannitol, 21

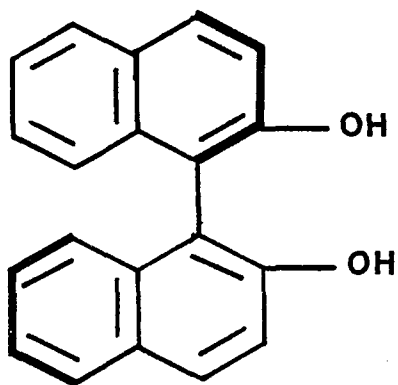


1,4:3,6-Di-O-benzylidene-D-mannitol, 22

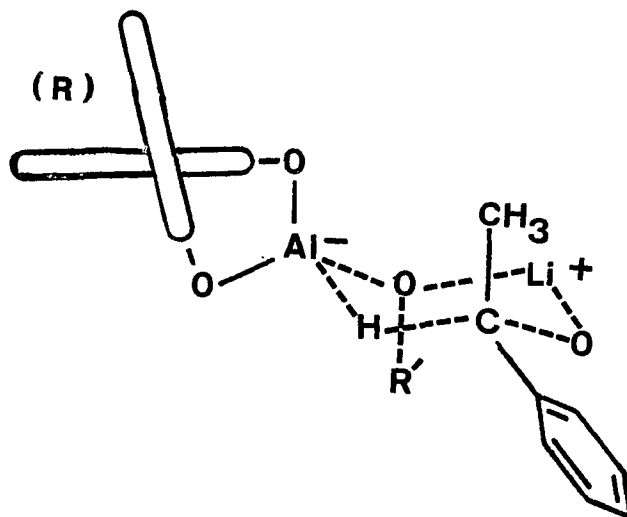
Despite the difficulties encountered in the diol studies discussed previously, the most generally efficient asymmetric diol-LAH reducing agent of any yet reported is that prepared using binaphthol, 23.³¹ Excellent optical yields have been reported for the reduction of several ketones using a chiral reagent prepared by treating LAH successively with 1 equivalent of ethanol then 1 equivalent of 23.³¹⁻³³ Complete enantioselectivity, i.e., 100% ee, was achieved in the reduction of butyrophenone by this reagent. A large effect of the secondary modifier was noted. When no ethanol was added only 2% ee of methylphenylcarbinol was obtained and there was a reversal in the sense of the stereoselectivity when more bulky achiral alcohols were used.

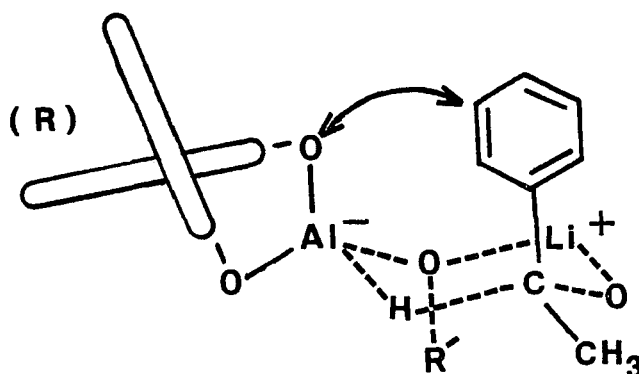
The stereochemical results were rationalized by diastereomeric six-membered cyclic transition states, 24 and 25. Using acetophenone as a model substrate 24 was presumed to be favored over 25, resulting in the formation of the alcohol having the R configuration. It was

speculated that the cause of the stereochemical reversal when bulky secondary modifiers were used was some kind of unspecified alteration of the transition state due to the increased steric bulk.



(R)-(+)-2,2'-Dihydroxy-1,1'-binaphthyl, 23

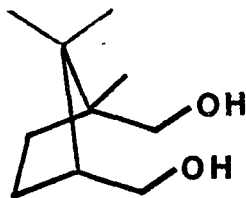




25

1,5-Diols

Johnson used the diol 26 as an LAH modifier in the reduction of propiophenone to determine what achiral alcohol is the most efficient secondary modifier.³⁴ 18.5% ee was obtained when isopropanol was used as the secondary modifier. This was superior to the results when methanol, ethanol, tert-butyl alcohol or benzyl alcohol were used. It was noted that there was a difference between the two hydrides of the proposed dihydride reagent. The use of a large excess of hydride to insure complete reduction was discouraged. Due to disproportionation of the alkoxyaluminum hydride, this practice results in an increased amount of more reactive achiral LAH species.



(+)-1,2,2-Trimethyl-1,3-bis(hydroxymethyl)cyclopentane, 26

Amine Modified Lithium Aluminum Hydride

Monoamines

Primary Monoamines

There is only one reported use of a simple optically active primary amine as an LAH modifier for ketone reductions*. Solladie' and co-workers obtained 14.2% ee of (R)-(-)-spiro-[4,4]-nonan-1-ol by reducing the corresponding ketone with 2-LAH/(+)-1-phenylethylamine.³⁶

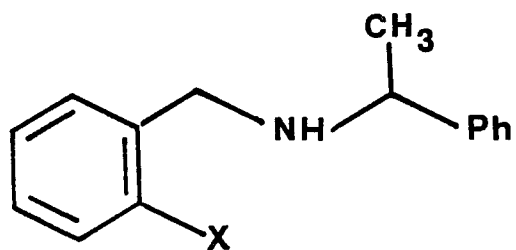
Secondary Monoamines

Yamaguchi and coworkers prepared a series of (S)-(-)-N-(O-substituted benzyl)-2-phenylethylamines, 27a-27f, and tested them as LAH modifiers in the reduction of acetophenone.³⁷ The best result, 43.0% ee (R), was obtained when 3 equivalents of 27c, X=NMe₂, were used. Under identical conditions, propiophenone was reduced with somewhat better stereoselectivity, 52% ee (R).

Some interesting behaviors were observed in the reduction of acetophenone with this series of ligands. Running the reduction at -78°C instead of 0°C resulted in decreased optical yields. In two cases, 3 equivalents of 27a, X=H, and 27e, X=Me, this change in reaction temperature resulted in a reversal in the direction of the stereoselectivity, R to S. In two cases, 27c, X=NMe₂, and 27d, X=OMe, the same selectivity change, R to S, occurred when the ratio of amine to LAH was changed from 2 or 3 to 1, and 2 to 3, respectively.

There are a few more features of this system that should be pointed out. At room temperature only 1 equivalent of H₂ was evolved. Upon re-

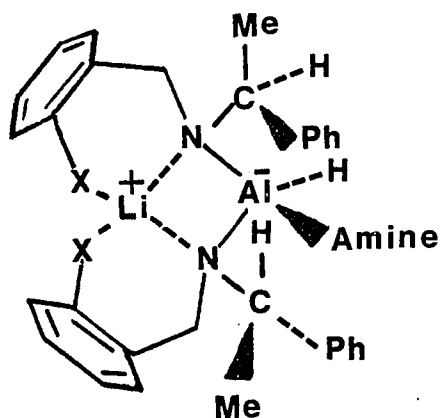
*This same reagent has been used to reduce racemic styrene oxide³⁵ but this was a kinetic resolution, not an asymmetric synthesis.

27

X=

- | | |
|---|------------------|
| a | H |
| b | Me |
| c | NMe ₂ |
| d | OMe |
| e | SMe |
| f | 2,4,6-Trimethyl |

fluxing, 1 or 2 more equivalents of H_2 were evolved depending on the amount of amine that had been used. The reactions were run in toluene (to eliminate possible coordination of the solvent) and all of these reagents were soluble even at $-78^\circ C$. A set of reductions containing potentially coordinating additives indicated that an ortho dimethylamine group (27c, $X=NMe_2$) changed the stereoselectivity, presumably via coordination with the Li cation. A structure of these complexes was proposed, 28.



28

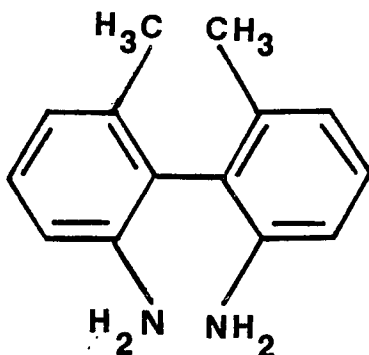
$X=NMe_2, OMe, SMe$

Diamines

Primary Diamines

Suda and coworkers studied the reduction of a variety of substrates with LAH modified by varying amounts of optically pure (R)-2,2'-diamino-6,6'-dimethylbiphenyl, 29.³⁸ The temperature of reagent formation, $20^\circ C$ to $-49^\circ C$, and the order of LAH and ligand addition as

well as the modifier/LAH ratio (1 to 3.4) were also varied. The highest optical yield, 54% ee, was obtained in the reduction of phenyl tert-butyl ketone by the reagent prepared by adding an ethereal LAH solution to a solution of the amine at -40°C (ketone/LAH/amine=1.4:1:2.1). It was found that addition of an LAH solution to the amine solution was preferable to the reverse order. Also, the reagent prepared at 20°C was totally ineffective as an asymmetric reducing agent and there was a trend towards higher optical yields with higher modifier/LAH ratios. It was concluded that at least three different reagents formed depending on the conditions (primarily temperature) under which the reagent was prepared.

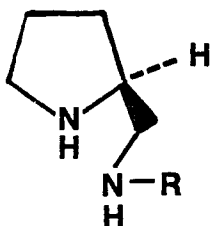


2,2'-Diamino-6,6'-dimethylbiphenyl, 29

Secondary Diamines

Mukaiyama and Asami investigated a series of (S)-2-(N-substituted aminomethyl)pyrrolidines derived from (S)-proline, 30a-30m, as LAH modifiers.³⁹⁻⁴¹ The chiral efficiency of this system was tested in different solvents, at different temperatures and with different LAH/ligand/ketone ratios. (S)-2-(2,6-xylylidinomethyl)pyrrolidine, 30m,

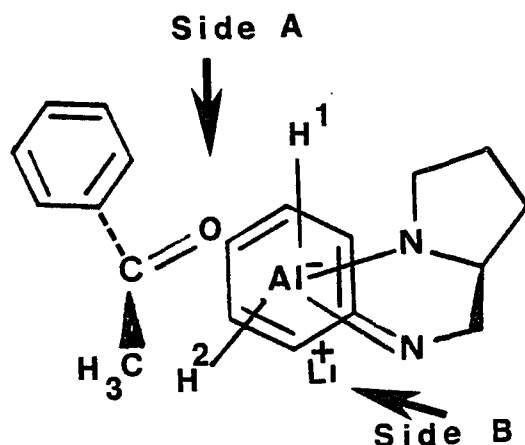
proved to be the most effective modifier. Propiophenone was reduced in 90% yield and 96% ee by LAH (2.5 equivalents)/30m (3.0 equivalents) in Et₂O at -100°C. All of the reagents were heterogeneous in ether. Modifiers in which R=aryl were generally superior. Addition of TMEDA, DME or MgBr₂ resulted in decreased optical yields suggesting that the Li cation was involved in the transition state.

30

R=		R=	
a	Ph	h	2-Methoxyphenyl
b	Isopropyl	i	4-Methoxyphenyl
c	Hexyl	j	2-Pyridyl
d	Cyclohexyl	k	4-Pyridyl
e	(<u>R</u>)-1-Phenylethyl	l	3,4-Dichlorophenyl
f	(<u>S</u>)-1-Phenylethyl	m	2,6-Dimethylphenyl
g	1-Naphthyl		

The effectiveness of this system was explained using a model, 31, in which the formation of a "sterically restricted cis-fused bicyclic hydride reagent"⁴⁰ created a new chiral center at the nitrogen atom. It was proposed that one of the two hydrides, H¹, in this reagent is

too hindered sterically to react with ketones. The author also proposed that approach of the ketone is blocked on one side, B, by the Li cation.*



31

3° Diamines

Perhaps the simplest and/or most esthetically appealing approach to amine modified LAH is to coordinate the Li cation of the hydride to the nitrogen of an optically active amine. This was done by Whitney and Langer.⁴⁴ A variety of substrates were reduced by the chelated reagent formed by treating 1 equivalent of LAH with 1 equivalent of either (R,R)-(-)- or (S,S)-(+)-N,N,N',N'-tetramethylcyclohexanediamine [(-)-or (+)-TMCHD], 32. Generally, low optical yields (less than 12% ee) were obtained. The reduction of 1-hydroxy-3-butanone, however, showed significant asymmetric induction (ca. 30% ee). This indicated

*In light of evidence that the Li cation actually activates the ketone for reduction in LAH systems^{42,43} this could be a tenuous proposal. In fact, the reactive hydride may be the one nearer the Li cation.

that there may be a significant effect on the chiral efficiency of the system when the substrate contains another group that is capable of reacting with the LAH reagent.

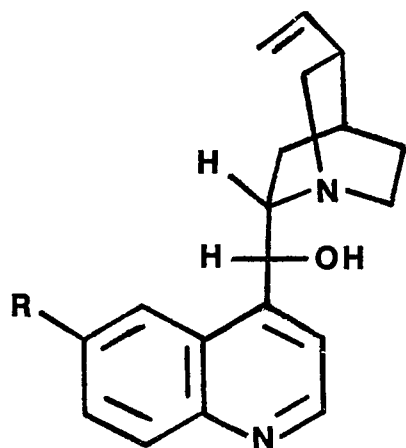
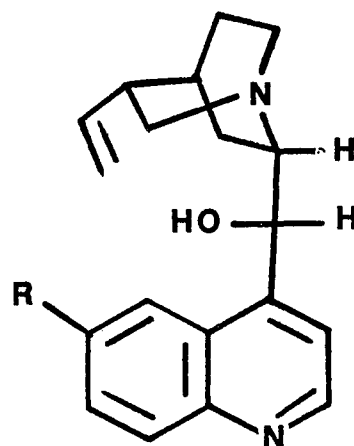
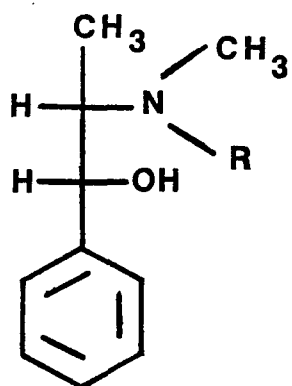
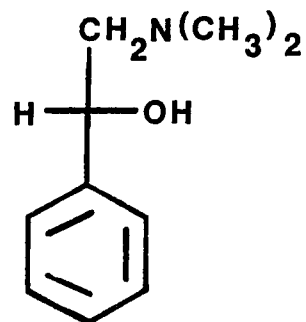
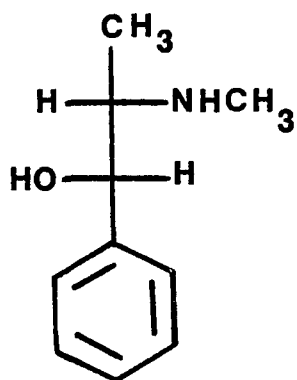


(S,S)-(+)-N,N,N',N'-tetramethylcyclohexanediamine, (+)-TMCHD, 32

Amino Alcohol Modified Lithium Aluminum Hydride

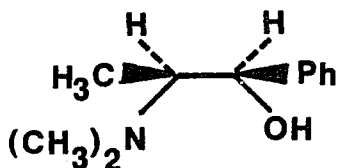
1,2-Amino Alcohols

Cervinka reported the modification of LAH with several naturally occurring amino alcohols, 33-37.¹⁶ The best result was obtained when acetophenone was reduced in 48% ee by LAH/(-)-quinine, 33a, in ether. In a rather intensive study of this system, the effects of solvent, temperature and cation variations were examined. Reversals in the direction of the asymmetric induction of acetophenone were noted when the solvent was changed from Et₂O to THF, when the cation was changed from Li to Na in THF and when the temperature was varied (with dioxane as the solvent). One of the conclusions that was drawn from this study was that asymmetric induction in such chirally modified LAH systems is enhanced whenever a nitrogen atom is present. It was presumed that the nitrogen coordinated to the aluminum. For the most part, Cervinka's interest in this system was simply as a means to stereochemical correlations. Therefore most of his work involved

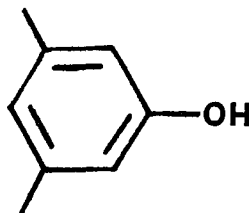
R=CH₃O, (-)-Quinine, 33aR=H, (-)-Cinchonine, 33bR=CH₃O, (+)-Quinidine, 34aR=H, (+)-Cinchonidine, 34bR=H, (-)-Ephedrine, 35aR=Et, (-)-N-Ethylephedrine, 35b(-)-1-Phenyl-2-dimethylaminoethanol, 36(+) -Pseudoephedrine, 37

the asymmetric reduction of a variety of substrates in an effort to determine the absolute configuration of the product.^{10,17,45-53}

Vigneron reported an extensive investigation of the use of (-)-N-methylephedrine, 38, as an LAH modifier.⁵⁴⁻⁵⁶ Several variables were examined: 38/LAH ratio, ketone, the use of achiral and chiral comodifiers and the effect of solvent, concentration, temperature and the rate of ketone addition. Of the 23 comodifiers tested, 3,5-xyleneol, 39, was the most effective. Asymmetric reductions in ether were found to give higher % ee values than those in THF, and somewhat better values than those in benzene or toluene. The concentration and rate of ketone addition had small but significant effects on the % ee obtained. One of the most notable findings of this study was the existence of a unique temperature effect. The highest optical yield was obtained at -15°C. However, there was a second but lower maximum, in the plot of % ee versus temperature, at -50°C. No concrete explanation of this phenomenon was offered. Up to 88.6% ee of the R alcohol was obtained in the reduction of butyrophenone by the LAH/38/39 (2 equivalents) system at -15°C in ether. Up to 90% ee (R) was obtained in the reduction of acetylenic ketones by the same reducing system.



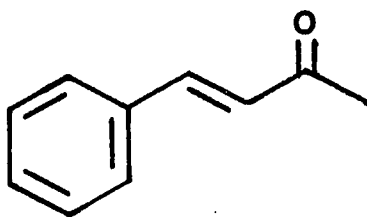
(-)-N-Methylephedrine, 38



3,5-Xyleneol, 39

In a search to find an effective asymmetric reducing agent for α,β -unsaturated ketones, Terashima and coworkers investigated LAH

modified by a series of N-alkyl-ephedrine plus N-alkyl anilines in a variety of solvents at various temperatures.⁵⁷⁻⁵⁹ It was found that reduction by LAH/(-)-N-methylephedrine, 38/N-ethylaniline (2 equivalents) in ether at -78 to -100°C gave the best optical yields. Using this reagent, propiophenone was reduced in 90% ee (S) and the α,β -unsaturated ketone shown, 40, was reduced in 98% yield and 98% ee (S). It is interesting to note that the configuration of the alkylphenylcarbinols obtained is opposite to that obtained by Vigneron using (-)-N-methylephedrine and 3,5-xyleneol. A transition state was proposed in which the nitrogen of the amino alcohol is coordinated to an octahedral aluminum atom.

40

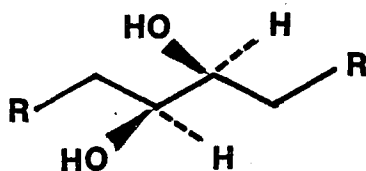
Seebach and coworkers prepared a series of tartaric acid derived diols, 41a-41i, which were tested as LAH modifiers for a variety of substrates.⁶⁰⁻⁶³ In an effort to maximize the optical yield, several variables were examined. It was found that excess hydride, changes in reaction time and addition of a second achiral modifier had only a small effect on optical yield. There was an increase in optical yield, but a decrease in chemical yield in the solvent series benzene,

ether, THF and dioxane. The preferred temperature varied with the solvent; % ee values were highest in ether at room temperature and in THF at reflux. Generally, optical yields of less than 50% ee were obtained, however, methyl mesityl ketone was reduced by LAH/41b in 87% ee. The use of the methyl ethers of 41a and 41g as chiral solvents resulted in decreased optical yields.

Although no definitive conclusions were drawn, some general proposals were made and possible mechanisms were discussed. Since an aged reagent produced higher optical yields, it was postulated that the more thermodynamically stable form of the reagent was the most effective in inducing asymmetry. The reagent was believed to be a cyclic monomer. The stereochemical results were rationalized via proposed transition states in which the Li cation was coordinated to either the carbonyl oxygen, the carbonyl oxygen and one hydride or the carbonyl oxygen and the alkoxy group of comodifier. Perhaps the most interesting mechanistic interpretation was the proposed "windshield wiper effect" or "kickout effect" of the amino groups in which the nitrogen assists hydride transfer to the Li coordinated ketone via a backside attack on the aluminum as shown, 42.

A (+)-camphor derived ligand, 43, with 2° amino and 2° alcohol groups has also been examined as an LAH modifier.⁶³ Up to 43% ee of the R alcohol was obtained in the reduction of acetophenone. Increasing the 43/LAH ratio from 1:1 to 1.1:1 and decreasing the temperature from -78 to -100°C each resulted in significant increases in the optical yield.

Chiral oxazolines, 44a-44d, have also been utilized as LAH modifiers.⁶⁴ After studying some variables in this system, it was found that the best results were obtained when LAH and 2 equivalents

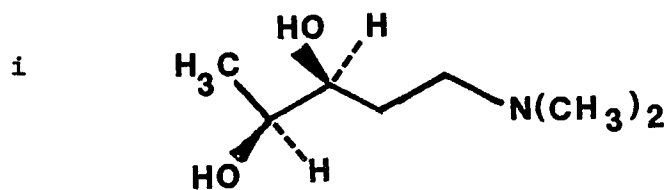
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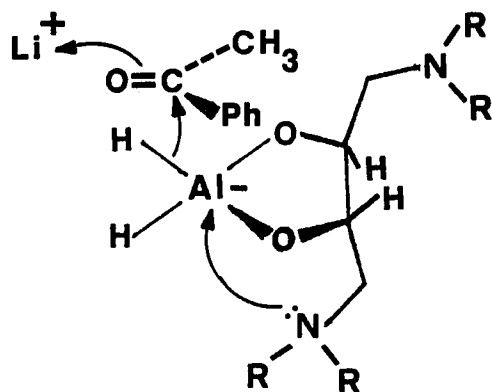
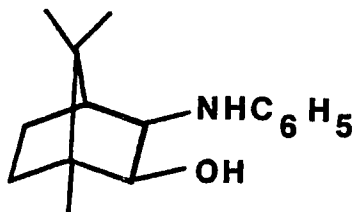
R=

a $N(CH_3)_2$

b Pyrrolidino

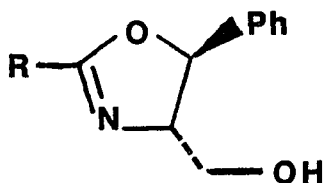
c Piperidino

d $N(CH_3)C_8H_{17}$ e $N(CH_3)C_6H_5$ f $N(CH_3)-[CH_2CH_2O]-CH_3$ g OCH_3 h OC_6H_5 

42

(+)-(1R,4S)-Exo-anilino-2-exo-hydroxybornane, 43

of 44 were used at -78°C in THF. Under these conditions 1-phenyl-ethanol (R) was obtained in 65% ee. With regard to this reagent it is interesting to note that the 4th hydride was unreactive toward ketone.



44

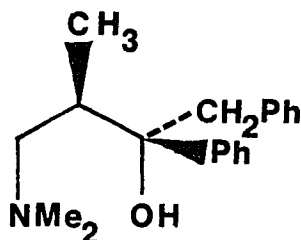
R=

- a Me
- b Et
- c i-Pr
- d PhCH_2

1,3-Amino Alcohols

The most interesting reagent reported to date is that from LAH modified with Darvon alcohol, 45.⁶⁵⁻⁶⁷ Reduction of acetophenone within 3 minutes after mixing 2.3 equivalents of Darvon alcohol with 1 equivalent of LAH (in ether at 0°C) produced 68% ee of (R)-(+)-methylphenylcarbinol. If this reagent was aged for increasing lengths of time, an increasing amount of the S isomer was produced. When the reagent prepared as above was refluxed for 10 minutes then allowed to stand overnight a maximum of 66% ee of the S isomer was reached. Up to 75% ee of (R)-or (S)-methylphenylcarbinol was obtained by varying molar ratios and reaction temperature. The most conspicuous observations concerning this unique time-dependent reversal are that the

"R" reagent was a precipitate and the "S" reagent was soluble. The latter always resulted in incomplete reduction even when present in large excess. Despite a rather intensive investigation the exact cause of the reversal has not been pinpointed.

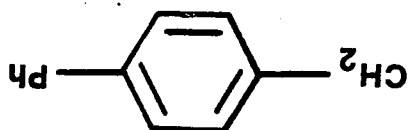


Daryon Alcohol, 45

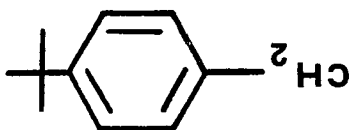
In a continuation of the Darvon study, Reich prepared a series of amino alcohols, 46-61, similar to Darvon alcohol and tested their efficiency as LAH modifiers.⁶⁸ In the reduction of acetophenone only two of these carbinolamines gave enantiomeric excesses comparable to that obtained with Darvon alcohol; 47 gave 75% ee (S) and 48 gave 77% ee of the S isomer. Three of the modifiers, 49, 51, and 53 resulted in modest optical yields (45-62% ee). All other ligands were inefficient modifiers; less than 33% ee was obtained with them.

Employing a slight modification of Mosher's procedure, Brinkmeyer and Kapoor were able to obtain up to 85% ee in the reduction of acetylenic ketones.⁶⁹ Ketone was added to fresh reagent over 30-60 minutes. As in the reduction of phenyl alkyl ketones, R alcohols were obtained in every case suggesting that the acetylenic bond has a steric and/or electronic effect similar to that of the phenyl ring.

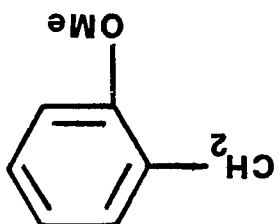
Cohen and coworkers used Darvon alcohol and a series of structurally related synthetic amino alcohols, 62a-62g, as LAH modifiers in



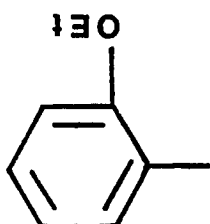
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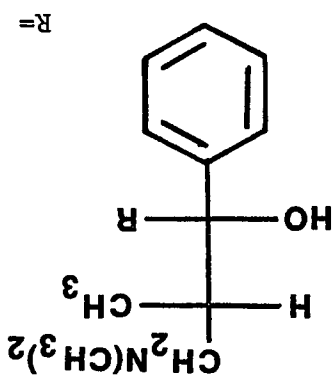
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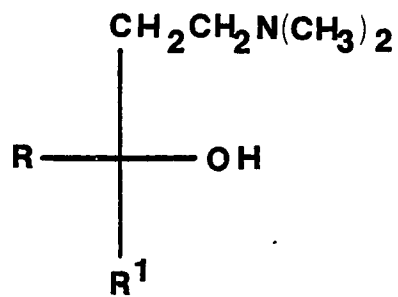


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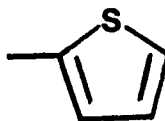
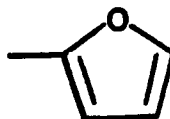
R=

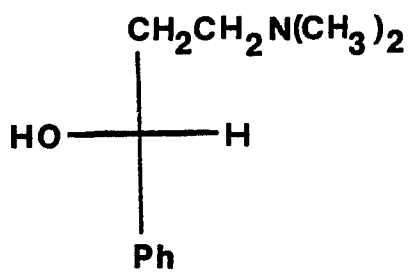
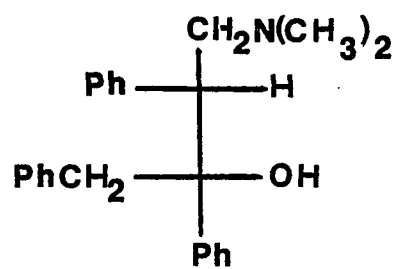
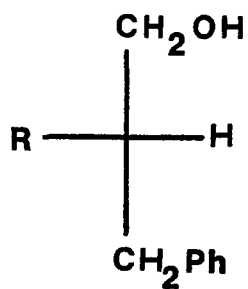
R¹=50

H

C(CH₃)₃51CH₂Ph

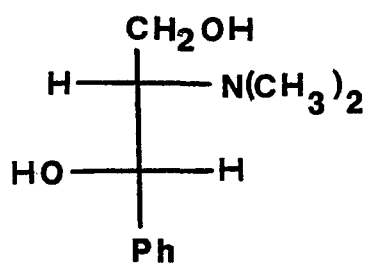
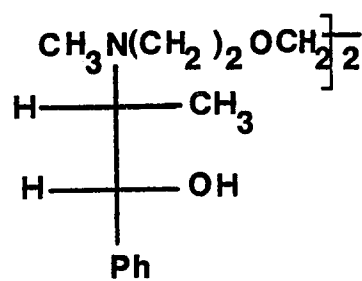
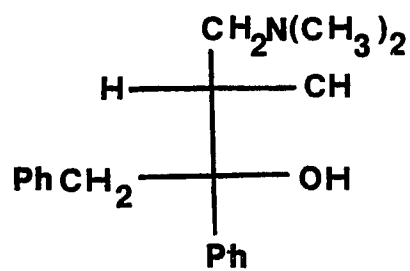
Ph

52CH₂Ph53CH₂Ph

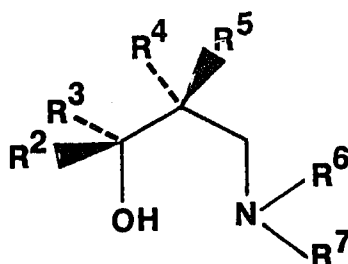
5455

R=

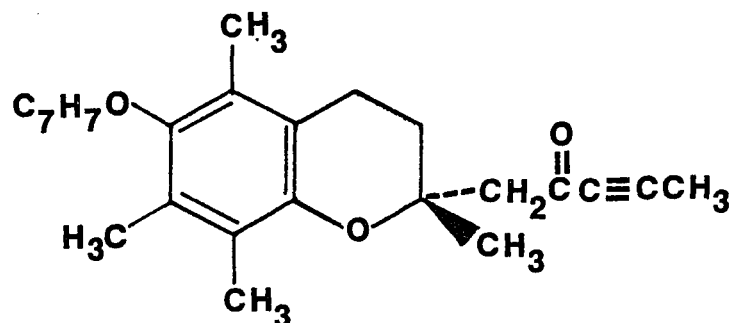
56 NH_2 57 NHCH_3 58 $\text{N}(\text{CH}_3)_2$

596061

reductions of α,β -acetylenic ketones.⁷⁰ Generally low optical yields (less than 36% ee in every case but one) were obtained using the synthetic ligands. A vitamin E precursor, 63, was reduced in 90% ee when Darvon alcohol, 62a, was used. In the reduction of acetophenone, using synthetic amino alcohol 62c, the optical yield obtained, 60% ee (S), was comparable to that obtained with Darvon alcohol. Since the configuration of the carbinols obtained via the synthetic ligands was opposite that obtained when Darvon alcohol was used, it was concluded that the secondary methyl group of Darvon alcohol was responsible for a significant amount of the asymmetric induction. No transition state or mechanistic speculations were offered.

62

	<u>R²</u>	<u>R³</u>	<u>R⁴</u>	<u>R⁵</u>	<u>R⁶</u>	<u>R⁷</u>
a	PhCH ₂	Ph	CH ₃	H	CH ₃	CH ₃
b	Ph	PhCH ₂	H	CH ₃	CH ₃	CH ₃
c	H	H	CH ₃	H	CH ₃	CH ₃
d	H	H	CH ₃	H	CH ₃	(<u>S</u>)-CH(CH ₃)Ph
e	H	H	H	CH ₃	CH ₃	(<u>S</u>)-CH(CH ₃)Ph
f	H	H	CH ₃	H	PhCH ₂	PhCH ₂
g	H	H	CH ₃	H	---(CH ₂) ₄ ---	

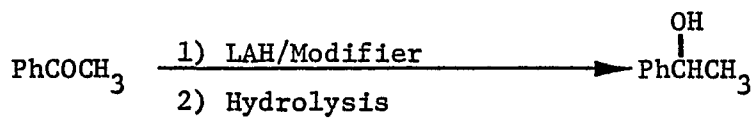


Summary and Remarks

Tables 1 and 2 are intended to provide a summary of the best results obtained in the reduction of phenones. Only those systems that gave better than 70% ee in the reduction of acetophenone are listed. Although the conditions under which these results were obtained varied, two generalities are apparent. All of these chiral modifiers are bidentate. Also, the generally more effective modifiers (23 plus EtOH, 30a and 30m) can form two covalent bonds to aluminum as distinct from the other ligands (except 19c) which are bidentate by way of one covalent bond and one coordinating heteroatom. These facts may substantiate a previously stated assumption that bidentate ligands disproportionate to a lesser extent than monodentate ligands thereby resulting in more reduction by chirally modified LAH species than by achiral LAH. On the other hand, the greater stereoselectivity obtained with these modifiers may simply be a result of the formation of a more rigid reducing complex. Whatever the reason is, it is clear that a bidentate structure is essential to the design of an effective LAH modifier.

Table 3 is a summary of some results obtained in the three studies to date of the reduction of acetylenic ketones. Generally, such studies

Table 1. Reduction of acetophenone by the more efficient modified LAH reagents.^a

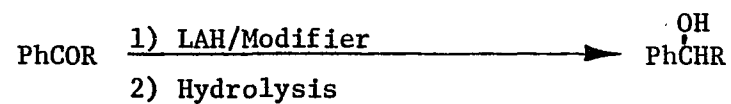


<u>Modifier</u> ^b	<u>Product</u> % ee (configuration)	<u>Reference</u>
<u>19c</u> + EtOH	71 (<u>R</u>)	26
<u>23</u> + EtOH	95 (<u>R</u>)	31
<u>30a</u>	92 (<u>S</u>)	39,40
<u>30m</u>	95 (<u>S</u>)	41
<u>38</u> + <u>39</u>	84 (<u>R</u>)	54,55
<u>38</u> + PhNH ₂ t	88 (<u>S</u>)	57
<u>45</u>	75 (<u>R</u> or <u>S</u>)	65,66
<u>47</u>	75 (<u>S</u>)	68
<u>48</u>	77 (<u>S</u>)	68

^aThis table is intended as a general overview of results greater than 70% ee.

^bVarious ligand/LAH/substrate ratios, solvents and temperatures were employed.

Table 2. Reduction of some phenyl alkyl ketones by the more efficient modified LAH reagents.^a



Product % ee (configuration)						
Ketone	<u>PhCOEt</u>	<u>PhCOPr</u>	<u>PhCOBu</u>	<u>PhCOi-Pr</u>	<u>PhCOt-Bu</u>	<u>Reference</u>
<u>Modifier</u> ^b						
<u>19c</u> + EtOH	46 (<u>R</u>)	----	----	----	----	26
<u>23</u> + EtOH	98 (<u>S</u>)	100 (<u>S</u>)	100 (<u>S</u>)	71 (<u>S</u>)	----	31
<u>30a</u>	85 (<u>S</u>)	----	----	57 (<u>S</u>)	----	40
<u>30m</u>	96 (<u>S</u>)	----	----	89 (<u>S</u>)	----	41
<u>38</u> + <u>39</u>	85 (<u>R</u>)	89 (<u>R</u>)	78 (<u>R</u>)	17 (<u>R</u>)	31 (<u>R</u>)	54
<u>38</u> + PhNH ₂ Et	90 (<u>S</u>)	----	80 (<u>S</u>)	78 (<u>S</u>)	----	57
<u>45</u>	----	62 (<u>R</u>) 59 (<u>S</u>)	----	30 (<u>R</u>) 48 (<u>S</u>)	36 (<u>R</u>) 9 (<u>S</u>)	66

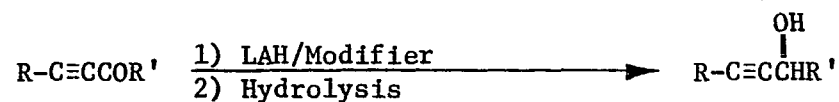
Table 2 continued.

Ketone	Product % ee (configuration)					Reference
	<u>PhCOEt</u>	<u>PhCOPr</u>	<u>PhCOBu</u>	<u>PhCOi-Pr</u>	<u>PhCOt-Bu</u>	
<u>Modifier</u>						
<u>47</u>	----	----	----	----	18 (<u>S</u>)	68
<u>48</u>	----	----	----	----	27 (<u>S</u>)	68

^aThis table is intended as a general overview of results obtained using the ligands listed in Table 1.

^bVarious ligand/LAH/substrate ratios, solvents and temperatures were employed.

Table 3. Some acetylenic ketones reduced with high stereoselectivity by amino alcohol modified LAH.^a



R/R'	Product % ee (configuration)				<u>63</u>	<u>Reference</u>
	<u>H/C₅H₁₁</u>	<u>H/t-Bu</u>	<u>CH₃/i-Bu</u>	<u>C₅H₁₁/C₅H₁₁</u>		
<u>Modifier</u>						
<u>45</u> ^b	72 (<u>R</u>)	----	82 (<u>R</u>)	62 (<u>R</u>)	--	69
<u>45</u> ^b	----	----	82 (<u>R</u>)	----	90 (<u>R</u>)	70
<u>38</u> + <u>39</u> ^c	84 (<u>R</u>)	90 (<u>R</u>)	88 (<u>R</u>)	----	--	56

^aThis table is intended to provide a comparison of the three published attempts to reduce acetylenic ketones asymmetrically.

^bThe procedure used was essentially Mosher's^{65,66} (i.e., Darvon alcohol/LAH=2.3:1) except the reduction was run at Dry ice/acetone temperature.

^c38/39/LAH ratio was 1:2:1 and the reduction was run at -15°C.

have been used to find an effective reagent for the asymmetric reduction of a particular substrate, such as ketone 63. The substrates listed in Table 3 are only those which might allow one to compare the effectiveness of the three systems listed. A comparison of the results in Table 3 with results in Tables 1 and 2 for the same modifier indicates that the direction of the asymmetric induction in the reduction of acetylenic ketones is the same as in the reduction of phenones. This suggests, as was previously stated, that the phenyl ring and acetylenic bond behave as if they have similar steric and/or electronic parameters. Also, the degree of asymmetric induction achieved in the reduction of acetylenic ketones is somewhat greater than that obtained with the phenones. From Table 3 it appears that the N-methylephedrine/3,5-xyleneol system is somewhat more effective than is modification by Darvon alcohol.

Modified Sodium Borohydride

The modification of sodium borohydride, NaBH_4 , by chiral compounds has two important advantages over the modification of LAH. One feature is the lower cost of NaBH_4 . Equally important is the greater selectivity of borohydride reagents. This allows for more convenient handling procedures as well as compatibility with functional groups that would be attacked by LAH reagents.

There are relatively few examples of chiral borohydride reagents ⁷¹⁻⁸⁵, and generally, low ee values (less than 55%) have been obtained in ketone reductions. Up to 78% ee was obtained in the reduction of propiophenone using NaBH_4 in the presence of bovine serum albumin in a borax-buffered aqueous solution.⁷¹ This system may not, however, actually involve a modified borohydride reagent. The asymmetric in-

duction may be due primarily to binding of the substrate to the protein.

Several of the reported chiral borohydride reagents were formed by treating boranes with alkyl lithium reagents⁷⁹⁻⁸⁵. Since these reagents were not formed from NaBH_4 , a major potential advantage of the use of borohydride reagents (low cost) is lost. The use of boranes and alkyl lithium reagents would also present some handling problems in scale-ups.

The work that will be reported in this thesis concerning the modification of borohydride is of lesser importance than that concerning the modification of LAH. For this reason only this brief discussion of modified NaBH_4 has been added to the end of this first section. The borohydride work however actually lead to the more successful LAH modification and will therefore be discussed first in the following section.

II. RESULTS AND DISCUSSION

Chiral Potassium Borohydride

In this study a chiral borate hydride was prepared by treating tris[(S)-2-hydroxypropyl]borate with solid KH in refluxing THF. This reagent was used to asymmetrically reduce propiophenone to methylphenylcarbinol in 14% ee.

Isopropyl borate reacts with an excess of solid potassium hydride in THF to give a quantitative yield of potassium triisopropoxyborohydride (KTPBH).^{86,87} As part of a broad based survey to find chiral borates that would behave similarly, it was found that triisopropanolamine borate⁸⁸, 64, reacted with excess KH in refluxing THF to give a quantitative yield of potassium triisopropanolamine borate hydride (TIPABH), 65, Figure 3.

When 2-methylcyclohexanone was reduced with TIPABH the resulting 2-methylcyclohexanol was a mixture of cis and trans isomers in a ratio of 72:28*. As a point of reference the same ketone was reduced by potassium triisopropoxyborohydride (KTPBH). The cis/trans diastereomer ratio of the alcohol produced was 89:11. Although there are similar groups attached to the boron in each reagent, those in TIPABH are tied back away from the boron by the nitrogen atom. This causes less steric hindrance in TIPABH than in KTPBH and results in a less stereoselective reduction. The lower stereoselectivity of TIPABH could also be related

*The cis isomer is less thermodynamically stable and predominates only when bulky reducing agents are used. The cis/trans ratio is therefore a measure of the effective steric bulk of the reagent.

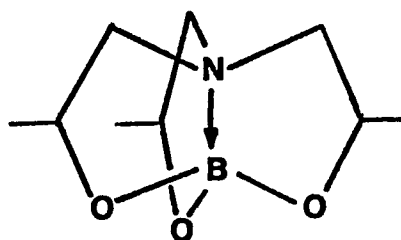
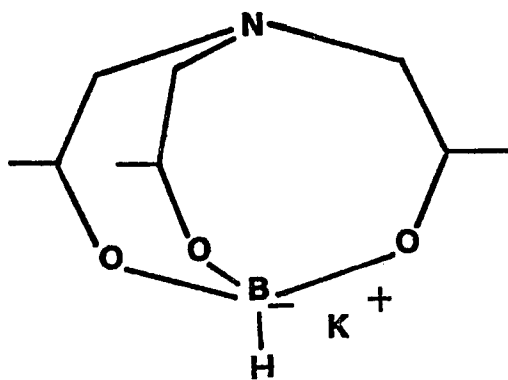
64KH
THF65

Figure 3. The preparation of TIPABH, 65.

in some way to transannular participation by nitrogen in the hydride transfer process.

Triisopropanolamine, TIPA, has three equivalent asymmetric centers and therefore exists as 4 optical isomers (2 diastereomeric pairs of enantiomers): R,R,R/S,S,S, (the "symmetrical diastereomers"⁸⁸) and R,S,S/S,R,R (the "unsymmetrical diastereomers"⁸⁸). Commercial TIPA is prepared from ammonia and racemic propylene oxide. Statistically it should be a 25:75 mixture of diastereomers. It has been found however that the ratio is actually 38.1:61.9.⁸⁸ Attempts to separate the symmetrical from the unsymmetrical isomers via recrystallization of the triol and the borate were only partially successful⁸⁸. An attempt to effect a separation via the differential rates of hydrolysis of the borates* also failed.⁸⁸

Theoretically, either of two approaches could be used to obtain an optically pure isomer of TIPA. A commercial sample of TIPA containing all four stereoisomers could be separated and resolved or one of the isomers could be prepared from chiral precursors. Considering the unsuccessful attempts to separate the two diastereomeric racemates, the latter approach appeared to be the more promising. If optically pure TIPA is to be prepared via the same reaction that is used to make the commercial mixture of diastereomers (i.e., reaction of ammonia with 3 equivalents of propylene oxide) all that is necessary for the synthesis is optically pure propylene oxide.

Two methods were used to prepare (S)-propylene oxide from (S)-ethyl lactate, 66, a readily available and inexpensive starting material. The

*The borate of the symmetrical isomer hydrolyzes 138 times faster in water than that of the unsymmetrical isomer.⁸⁸

Elie1-Furst method,⁸⁹ outlined in Figure 4, involved THP protection of the hydroxyl group of the ester followed by LAH reduction to the mono-THP protected propylene glycol, 68. The unprotected 1° hydroxyl group was tosylated, then the THP protecting group was removed. Treatment of the 1° tosylate, 70, with KOH resulted in ring closure to the optically active oxide, 71. The overall yield (from lactate) reported by Elie1 and Furst was about 31%.

Two steps in the sequence were primarily responsible for the low yield. Elie1 and Furst observed that the removal of the THP group by methanolic HCl gave a 66% crude yield and the final ring closure proceeded in only a 58% yield. In this work, removal of the THP group was accomplished in nearly quantitative yield (thereby increasing the total yield to about 40%) by treating the THP protected tosylate, 69, with a catalytic amount of acidic ion exchange resin (Dowex 50) in methanol. An interesting observation was made with regard to this procedure. Complete deprotection could be accomplished only by two successive treatments with resin. Simply increasing the amount of ion exchange resin, the volume of MeOH and/or the reaction time was not sufficient to afford complete deprotection.

The yield in the ring closure was not improved upon. Presumably, the cause of this low yield is nucleophilic attack by OH⁻ on the 1° carbon bearing the tosylate group and/or on the 1° position of the oxide, both events resulting in the formation of propylene glycol. Although this situation might be remedied by the use of a non-nucleophilic base such as NaH, a shorter, less expensive strategy than the THP protection-tosylation-deprotection sequence was sought.

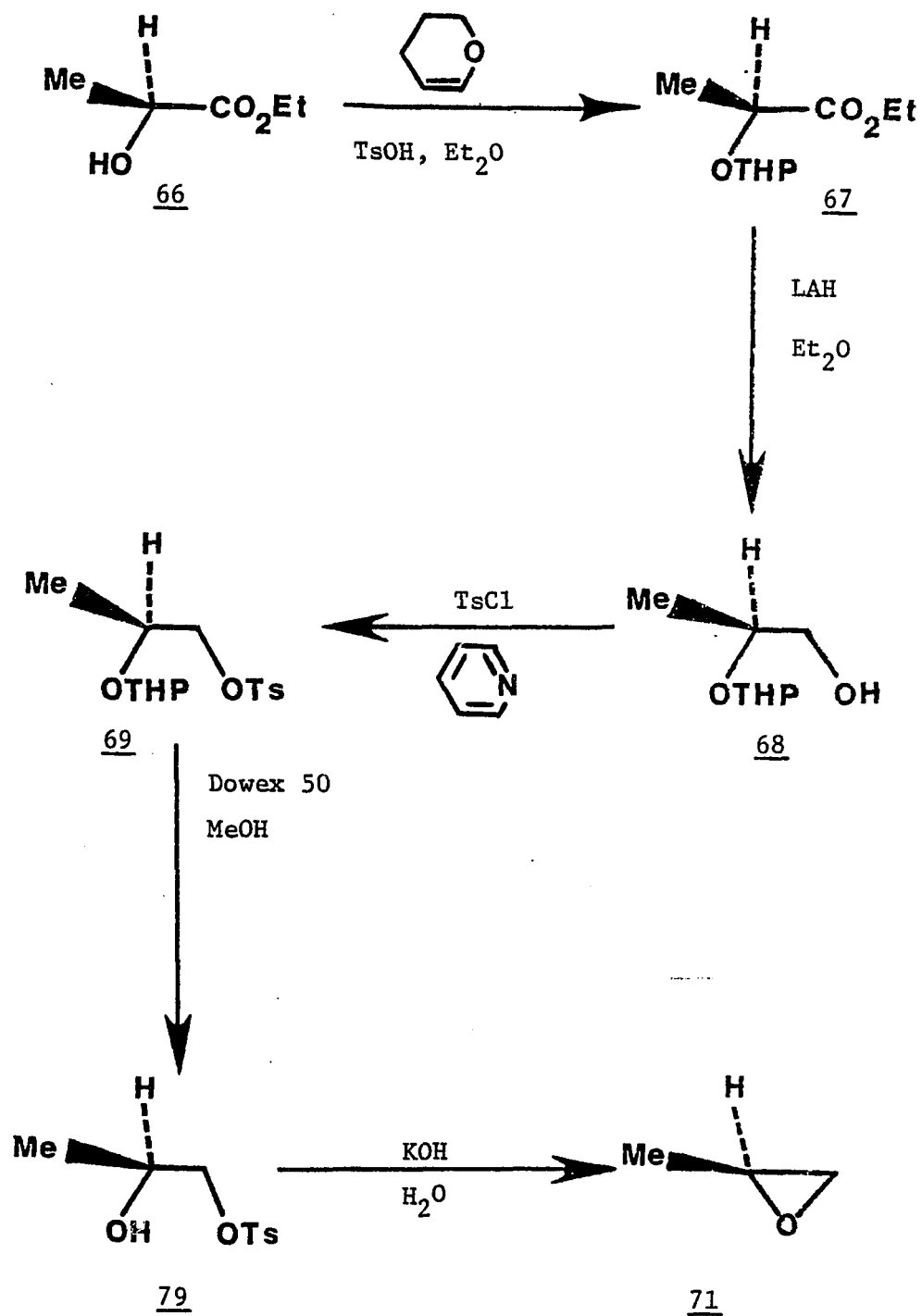


Figure 4. The preparation of (S)-propylene oxide by the Eliel-Furst procedure.

The overall yield of (S)-propylene oxide from (S)-ethyl lactate, 66, was increased to 65% by using the method of Golding et al. (Figure 5).⁹⁰ (S)-Lactate was reduced by LAH to (S)-propylene glycol, 72, which was treated with HBr/AcOH to give a mixture of (S)-2-acetoxy-1-bromopropane, 73, and (R)-1-acetoxy-2-bromopropane, 74. Golding reported a 95:6 ratio of 73 to 74, but in this work the presence of 74 was barely evident from the NMR spectrum of the product. The exact ratio is inconsequential, however, since both isomers are converted to (S)-propylene oxide, 71 on treatment with potassium pentoxide in 1-pentanol. Up to an 82% yield of (S)-oxide was obtained in the ring closure step of this sequence.

Although this was the method used to prepare most of the 71 used in this study, there are two drawbacks to the scale-up of this procedure. The extent of the scale-up that can be accomplished safely is limited somewhat by the LAH reduction step. Also, the relatively high cost of the HBr/AcOH used in step 2 could be intimidating if a significant scale-up is contemplated.

NaBH_4 has been used to reduce methyl lactate⁹¹ and could provide a safer alternative to LAH for large-scale work. Seeley and McElewee have obtained halohydrin benzoates by treating benzaldehyde acetals of 1,2,-diols with NBS⁹² and Barnett has prepared the bromo benzoate of propylene glycol by the same method.⁹³ Although this approach requires 2 steps for ester formation from the diol rather than 1, it is less expensive. Incorporating these modifications into the Golding procedure, should provide a reasonably safe, convenient and cost effective procedure for the large scale preparation of chiral propylene oxide (Figure 6).

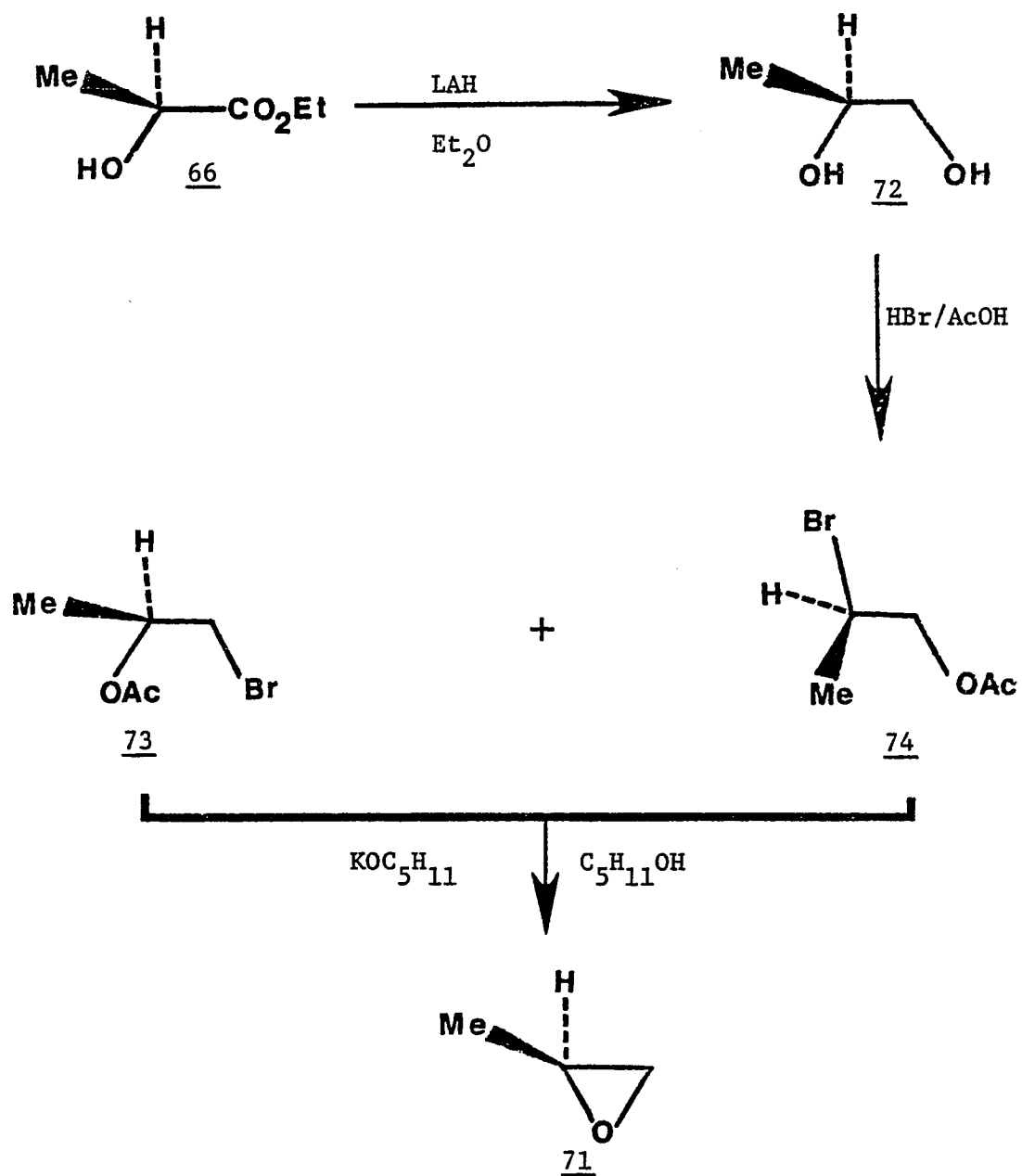


Figure 5. The preparation of **71** via the Golding method.

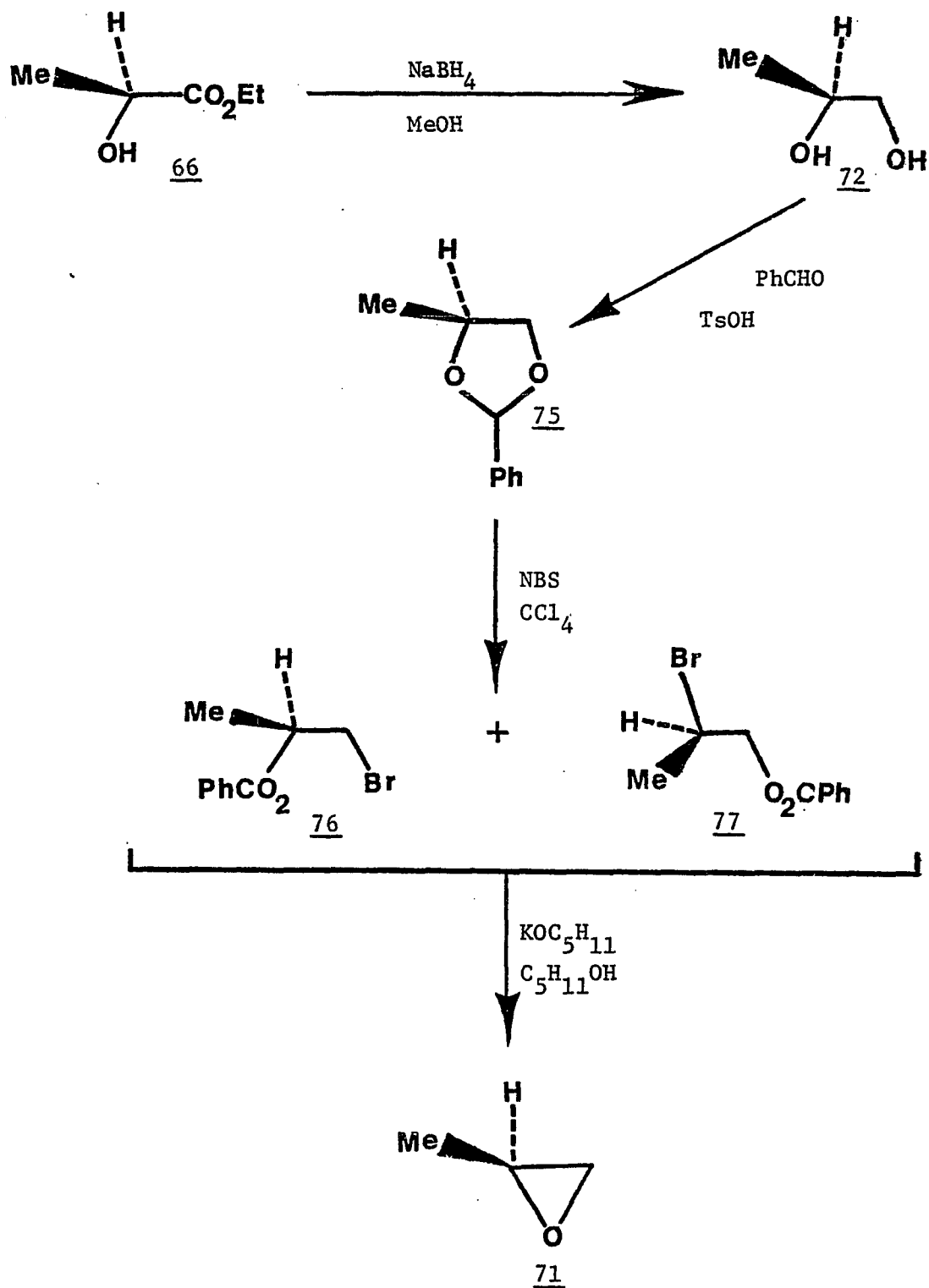


Figure 6. A proposed procedure for the large scale preparation of (S)-propylene oxide.

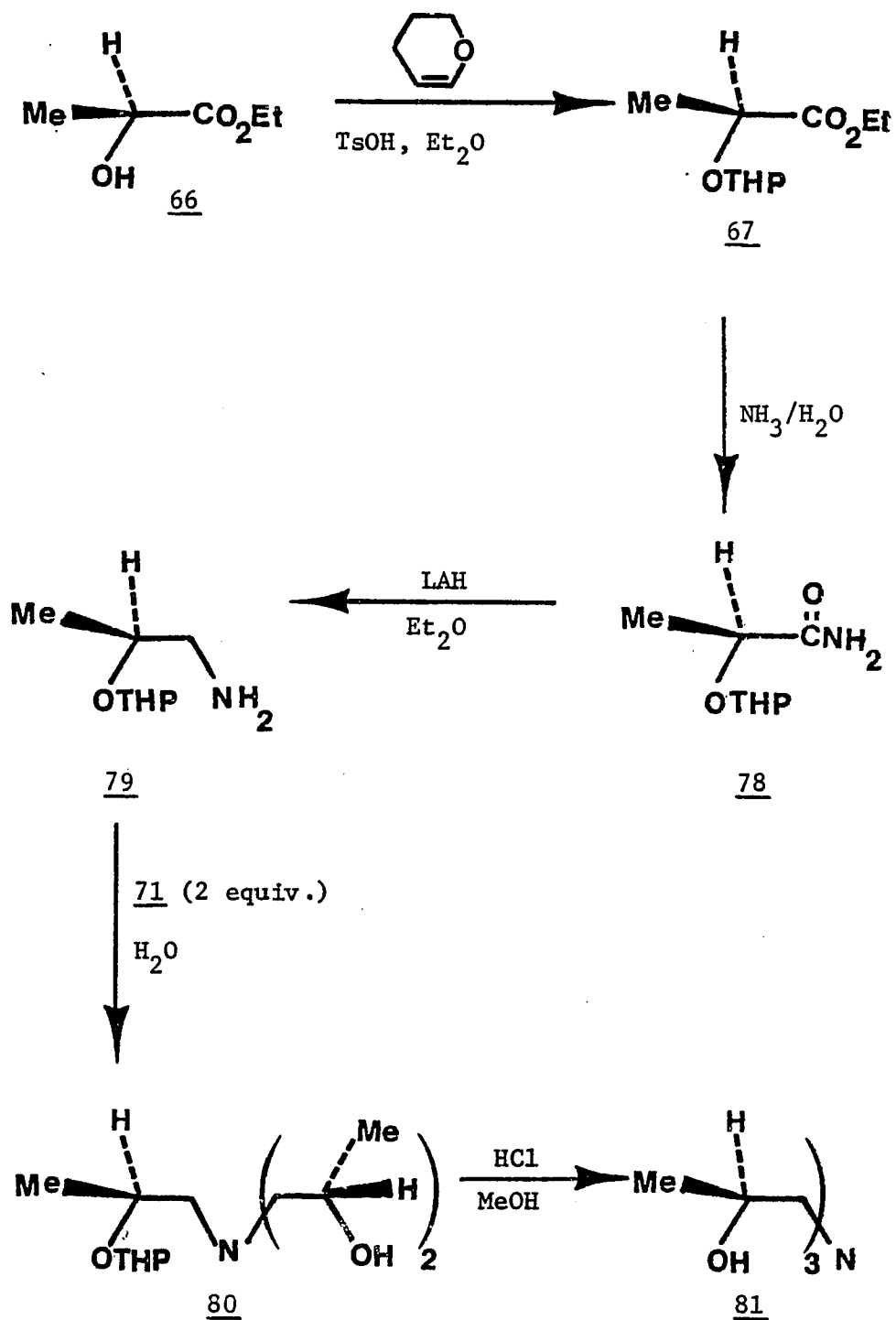


Figure 7. The preparation of (S,S,S)-TIPA via method A.

Two approaches to the preparation of optically active TIPA were used. In the first method, A (Figure 7), (S)-ethyl lactate, 66, was converted to the THP protected ester, 67 (as in Figure 4) which was subsequently treated with aqueous ammonia to produce the THP protected amide, 78. This was reduced with LAH to THP protected 1-amino-2-propanol, 79. Allowing 79 to react with 2 equivalents of the optically active oxide, 71, resulted in the formation of the mono-THP protected (S,S,S)-TIPA, 80. Removal of the protecting group with concentrated HCl in MeOH afforded (S,S,S)-TIPA, 81, in a low overall yield (29%). The major cause for this low overall yield was a 45% yield in the LAH reduction step.

The THP protecting group was incorporated in this scheme for two reasons: It masks the 2° OH group and blocks possible ring opening on the oxide which would lead to polymeric materials. Also, it was thought the THP group would add sufficient bulk to the amine to insure that attack would occur only at the 1° carbon of the oxide. It was later discovered however that THP protection was not necessary.

The original purpose of the preparation of the (S)-1-amino-2-propanol derivative, 79, was to provide a route to an "unsymmetrical" optically active TIPA isomer. If this amino alcohol, 82, or its THP derivative, 79, were allowed to react with 2 equivalents of (R)-propylene oxide, 83, which is readily available from (S)-alanine⁹⁴, (S,R,R)-TIPA, 84, would result (Figure 8). This synthetic scheme has not yet been utilized however. The second and considerably simpler approach to the preparation of chiral TIPA was the reaction of aqueous ammonia with a little over 3 equivalents of 71, (Figure 9).

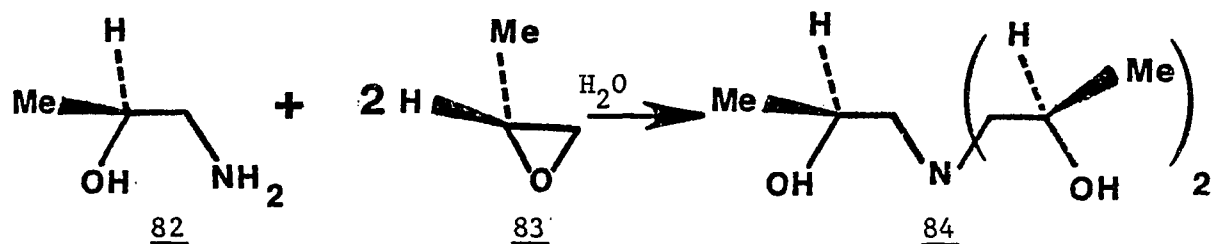


Figure 8. The proposed preparation of (S,R,R)-TIPA, 84

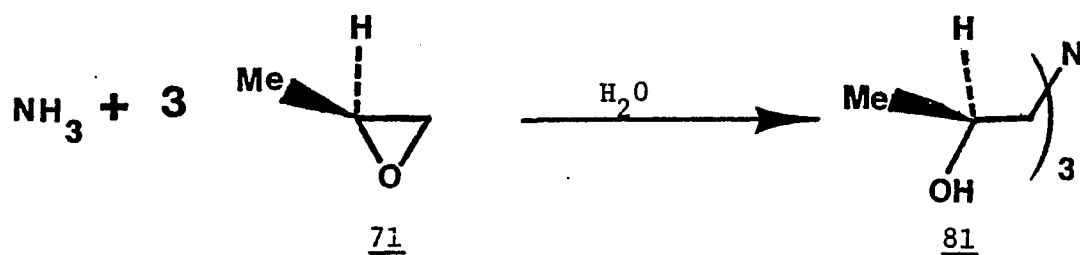


Figure 9. The preparation of (S,S,S)-TIPA via method B.

Although polymerization and attack by nitrogen on the 2° carbon of the epoxide in such systems reportedly do not occur to an appreciable extent,⁹⁵ there was a significant amount of an impurity in the TIPA from both methods of preparation. It was not determined whether this was a polymeric or an isomeric material, but since this by-product was produced in both methods, the THP group had essentially no effect.

(S,S,S)-Triisopropanol amine borate, 85, was prepared by azeotropic removal of water from the triol and boric acid in toluene (Fig. 10). The borate was refluxed with a mixture of KH in refluxing THF to produce the borate hydride, (S,S,S)-TIPABH, 86. Although this scheme worked well with the commercial TIPA diastereomeric mixture, the (S,S,S)-TIPA prepared via both methods A and B and the corresponding borate had broad m.p.'s. Also, difficulty was encountered in the formation of (S,S,S)-TIPABH. Extended refluxing was required and the uptake of KH was much less than expected. Reduction of propiophenone with this (S,S,S)-TIPABH resulted in only 37% reduction with 14% ee (R). Due to the poor chiral efficiency of this reagent, it was not studied further and the problems encountered in its preparation were not solved.

There are some plausible rationalizations for the synthetic difficulties encountered. The impurities in the (S,S,S)-TIPA may be different from those contained in the commercial material* and may not be removed during the borate preparation and recrystallization. Another problem was the hygroscopic nature of the borate. The initial preparation of TIPABH was done in February when there was low humidity. At that time achiral TIPAB appeared to be unaffected by atmospheric

*The commercial TIPA used contained 5% diisopropanolamine and < 0.05% monoisopropanolamine.

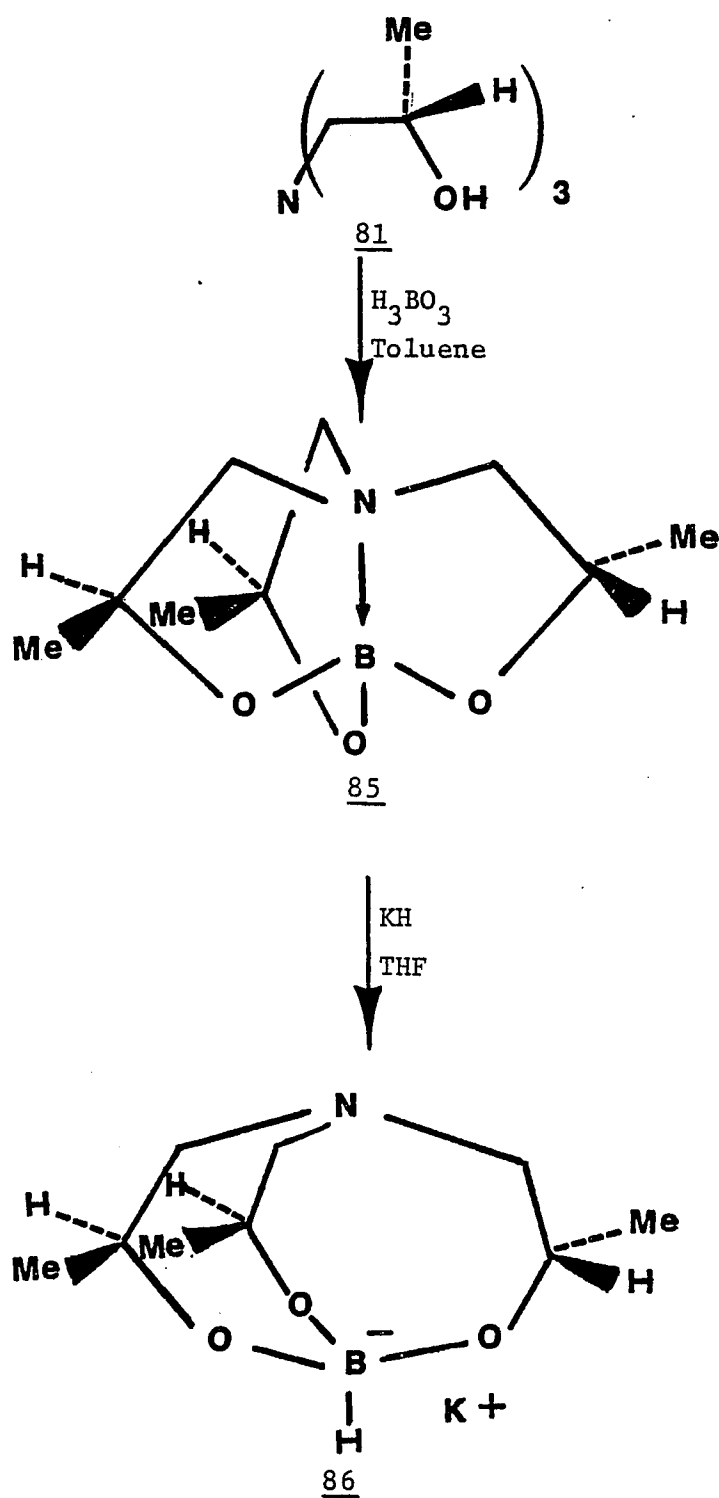


Figure 10. The preparation of (S,S,S)-TIPABH, 86.

moisture so no special precautions were ever taken to keep the borates in an anhydrous atmosphere. The chiral TIPAB, however was prepared in July when the humidity was very high. After the (S,S,S)-TIPABH reduction results were obtained it was found that the ester was actually deliquescent.

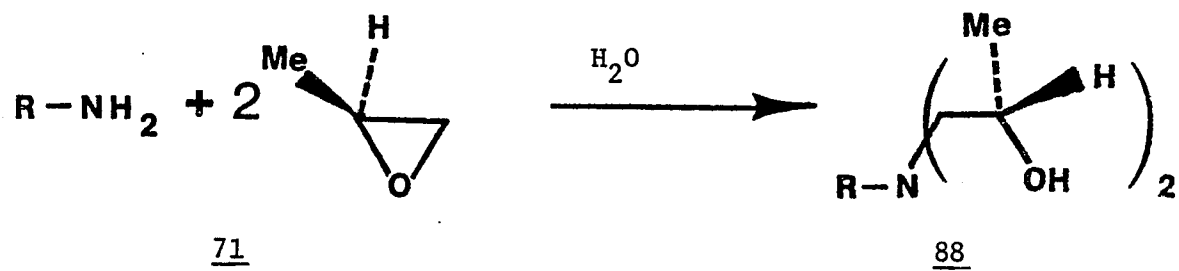
The low % ee obtained is not really very surprising. The cyclic structure of this reagent causes the methyl groups to be pulled away from the boron where the hydride transfer occurs. In addition (S,S,S)-TIPABH is probably too symmetrical to give good asymmetric induction.

Since it has been shown that (S,S,S)-TIPABH and TIPABH are effective reducing agents for ketones, it would probably be worthwhile to continue this study. One modification would be to replace methyl at the chiral center with other groups. This would best be accomplished by using other terminal oxides, 87, to prepare the corresponding triols. Of course if the alkyl groups are made too bulky, either the borate or the hydride may not form. In this work it has, for example, been found that trimethylborate does not form a hydride. Thus an extremely bulky R group such as tert-butyl should probably be avoided. A less symmetrical triol could be prepared by synthesizing the chiral unsymmetrical TIPA as described in Figure 8 or perhaps by simply treating ethanolamine with 2 equivalents of propylene oxide. Another approach to the design of such a borate hydride system could involve the synthesis of substituted tripropanolamine borates. In other words, by synthesizing a chiral aminotriol with the amine and alcohol functions in 1 and 3 positions relative to each other, a bicyclic borate containing two 10-membered rings, instead 8-membered rings as in TIPAB, could be prepared.

87R = Et, i-Pr, i-BuChiral Lithium Aluminum Hydride

If, instead of hydroxyalkylating ammonia with 3 equivalents of propylene oxide, a primary amine is allowed to react with 2 equivalents of propylene oxide, an N-substituted diisopropanolamine is produced.⁹⁶ In this manner a series of chiral diisopropanolamines, 88, were prepared (Figure 11). By treating (R)- α -methylbenzylamine with 2 equivalents of ethylene oxide, the chiral diethanolamine, 89, was also prepared.

Although (S,S,S)-TIPA was a relatively ineffective borohydride modifier, a preliminary evaluation of 88a as an LAH modifier in ketone



R=

- a n-Bu
 b t-Bu
 c (R)-PhCH(CH₃)
 d (S)-PhCH(CH₃)

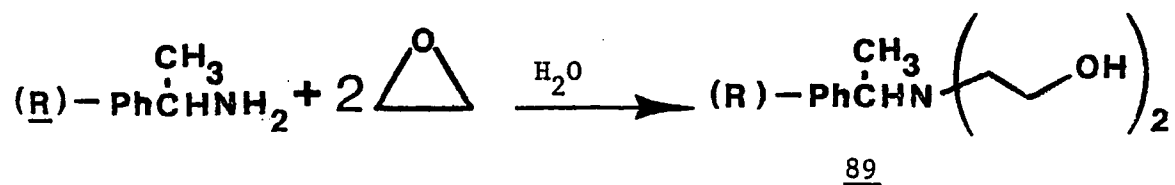
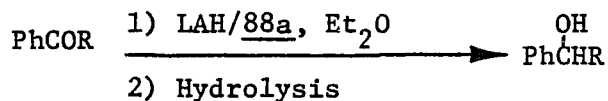


Figure 11. The preparation of chiral aminodiols from (S)-propylene oxide.

reductions (Table 4) indicated that this type of system had potential as an asymmetric reducing agent. Propiophenone and acetophenone were reduced in about 40% ee. The asymmetric induction decreased with 2-chloroacetophenone which was reduced in only 32% ee. Addition of a modifier (2-propanol) and the use of excess reagent were found to decrease the % ee (Reduction nos. 4 and 5 in Table 4). The low asymmetric induction (1% ee) when twice as much reagent was used was probably due to increased reduction by unmodified LAH from disproportionation as suggested by Johnson.³⁴ The reversal in the direction of the stereoselectivity is interesting, but probably not worth much speculation as to its origin because of the low ee value. The lower % ee obtained when the modifier was added more quickly, no. 6 vs no 1, may indicate that slower addition of the diol is preferable possibly due to the more predominant formation of a cyclic monomeric species. Nos. 6-9 provide a comparison of 4 possible procedures that were considered (see experimental). It is obvious that procedure D, no. 9, produces greater asymmetric induction. In this procedure the reagent was formed by addition of the modifier solution dropwise over minutes to a mixture of LAH in ether at 0°C. After cooling the mixture to -78°C, a solution of the ketone in ether was added dropwise over 5-10 minutes.

In order to try to standardize and optimize conditions in a convenient way two small changes were made in this procedure in subsequent reductions. The rate of the modifier addition was more accurately controlled so that it was completed over a 2 minute duration. Also, the length of time that the low temperature (-78°C) was maintained was conveniently controlled by simply filling a 2 L bath with dry ice/acetone. It was then about 7 hours before the temperature began to increase.

Table 4. Preliminary reductions with LAH modified by 87a.

Reduction No.	R	Procedure ^a	% Reduction	Product % ee ^b (Configuration)
1	Et	A ^c	100	41 (R)
2	Me	A ^c	100	38 (R)
3	CH ₂ Cl	A ^c	100	32 (R) ^f
4	Et	A ^d	36	16 (R)
5	"	A ^e	100	1 (S)
6	"	A	100	29 (R)
7	"	B	100	31 (R)
8	"	C	100	38 (R)
9	"	D	100	57 (R)

^aSee the experimental section for details.

^bThe % ee was calculated from the reported maximum rotation:
PhCH(OH)Et, $\alpha_D^{22} 29.16^\circ$ (neat)⁹⁷; PhCH(OH)Me, $\alpha_D^{22} 38.7^\circ$ (neat)⁹⁷;
PhCH(OH)CH₂Cl, $[\alpha]_D^{25} -47.8^\circ$ (c 2.8, cyclohexane)⁹⁸.

^cThe aminodiol solution was added over 15 min.

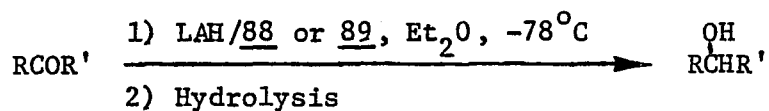
^dIsopropanol (1 equivalent) was added after the aminodiol had been added. The mixture was then stirred for 15 min before the ketone solution was added. Little gas was evolved in the workup.

^eA twofold amount of reagent was used.

^fAfter purification by prep. GC.

In Table 5 are summarized the results of the reduction of 3 substrates with LAH modified by each of the aminodiols. R carbinols were produced with 88a-88d except in the two anomalous reactions, 3 and 11, which were investigated and will be discussed later. The formation of acetylenic alcohols of the same configuration as the alkyl phenyl carbinols is in agreement with previous studies with other amino alcohol modifiers, suggesting once again that the phenyl ring and acetylenic bond have similar electronic and/or steric parameters.^{56,69,70} None of these ligands, however, appear to be as effective in the acetylenic ketone reductions as in the alkyl phenyl ketone reductions. This is in contrast to the results of several previous studies with other modifiers in which the asymmetric induction obtained with acetylenic ketones is generally equal to or superior to that obtained with phenones.^{56,69,70} Further discussion of this phenomenon will be reserved until later. Another trend which appears in this series of results and which also will be discussed later with additional results is the increased amount of S carbinol that is produced whenever reduction is incomplete, nos. 3, 7 and 11. The most dramatic example of this occurs with 88b, nos. 2 vs 3 and 10 vs 11.

Ligand 87a (nos. 1, 9 and 16) appears to be a fairly effective LAH modifier. Ligand 88b (nos. 2, 3, 10, 11 and 17) could be an excellent modifier if the source of the wild variation in enantioselectivity can be determined and controlled. Ligands 88c, 88d and 89 were designed specifically to probe the effect of chiral centers in the carbinol and noncarbinol "arms" of the modifier. From the results with 88a (nos. 1, 9 and 16), it appears that the S,S-diol moiety causes a substantial predominance of R carbinol. Nos. 8, 15 and 20 in which 89

Table 5. Reduction of ketones by LAH modified by 88a-88d and 89.^a

Reduction No.	Ketone	Modifier ^b	% Reduction	Product % ee ^c (Configuration)
1	PhCOEt	<u>88a</u>	100	57, 47 (<u>R</u>)
2	"	<u>88b</u>	100	83, 82 ^d (<u>R</u>)
3	"	"	66 ^e	32 (<u>S</u>)
4	"	<u>88c</u>	100	19 (<u>R</u>)
5	"	<u>88d</u>	100	77 (<u>R</u>)
6	"	"	100	68 (<u>R</u>)
7	"	"	59 ^e	34 (<u>R</u>)
8	"	<u>89</u>	100	10 (<u>S</u>)
9	PhCOMe	<u>88a</u>	100	44 (<u>R</u>)
10	"	<u>88b</u>	100	53 (<u>R</u>)
11	"	"	94 ^e	17 (<u>S</u>) ^f
12	"	<u>88c</u>	79 ^e	33 (<u>R</u>) ^f
13	"	<u>88d</u>	100	76 (<u>R</u>)
14	"	"	100	81, 82 ^d (<u>R</u>)
15	"	<u>89</u>	100	10 (<u>S</u>)
16	C ₅ H ₁₁ COC≡CH	<u>88a</u>	100 ^g	13 (<u>R</u>)

Table 5 continued.

Reduction No.	Ketone	Modifier ^b	% Reduction	Product % ee ^c (Configuration)
17	C ₅ H ₁₁ COC≡CH	<u>88b</u>	100 ^g	43 (<u>R</u>)
18	"	<u>88c</u>	100 ^g	19 (<u>R</u>)
19	"	<u>88d</u>	100 ^g	20 (<u>R</u>)
20	"	<u>89</u>	100 ^g	5 (<u>S</u>)

^aProcedure E was used in all reductions. See the experimental section for details.

^bSee Figure 11 for the structures.

^cThe % ee was calculated from the reported maximum rotation:

C₅H₁₁CH(OH)C≡CH, [α]_D 20.5° (c 2, Et₂O)⁵⁶; for α_D lit. of PhCH(OH)Et and PhCH(OH)Me see footnote b in Table 4.

^dAfter purification by prep. GC.

^eGas was evolved during the workup.

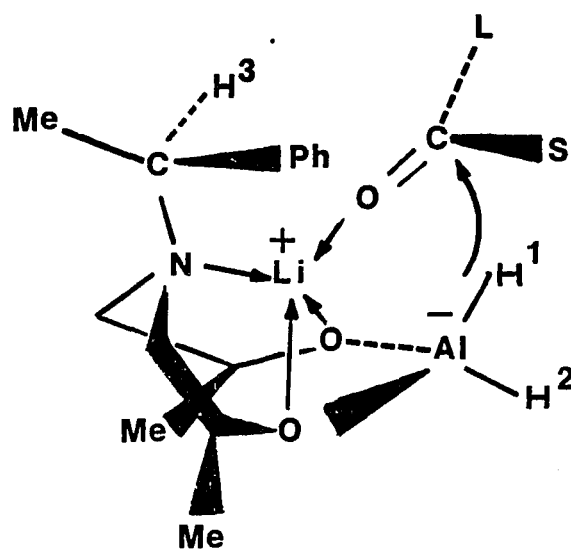
^f[α]_D lit. for the carbinol containing unreduced ketone was taken from reference 100.

^gDetermined via IR.

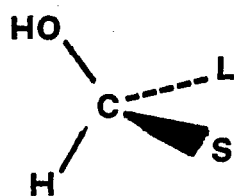
was used indicate that an (R)-2-methylbenzyl fragment results in the small but significant predominance of S carbinol. Ligand 88c, containing both S,S-diol and (R)-2-methylbenzyl moieties, induces the formation of R carbinols (nos. 4, 12 and 18) but to a lesser extent than the S,S-diol moiety alone in 88a. Quite surprising, however is the rather large enhancement effect observed when an (S)-2-methylbenzyl group is combined with an S,S-diol residue in 88d (nos. 5, 6, 7, 13, 14 and 19). This combination produces a large predominance of the R carbinol (up to 82% ee, no. 14).

The effectiveness of 88d can be rationalized using the stereocorrelation model shown in drawing 90. Since the reagent formed by adding 88d to an LAH solution is soluble in ether, it is assumed that it is a cyclic monomer.⁶¹ Although it is easier to see if a model is made, the nitrogen and the two oxygens of the model complex are perfectly positioned to coordinate with a Li cation which can also coordinate to one molecule of ketone. The bulk of the phenyl and methyl groups on the forward face of this stereocorrelation model would favor coordination of the ketone with the larger group (L) on the back side away from the ligand bulk. Subsequent transfer of H^1 to the ketone results in formation of the alcohol having the R configuration.

A similar model can be used to explain the lower % ee's obtained with the other ligands. With 88d, the phenyl group would be on the back face in opposition to the bulk of the methyl group on the front face resulting in decreased asymmetric induction. 88a, of course, does not contain a phenyl group so the asymmetric induction is due entirely to the positioning of the methyl groups, and 89 does not contain the methyl groups so with this ligand the induction is due entirely to the relative position of the phenyl group. Although the actual conformation



90

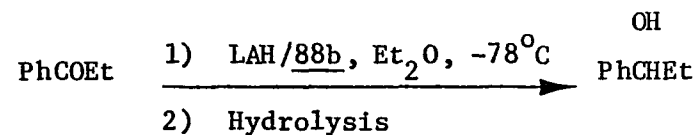


of the 2-methylbenzyl portion of the model is questionable, the effect of opposite configurations causes the % ee values to move in opposite directions clearly indicating that the amine portion is an important consideration in ligand design.

Ligand 88b is a special case. Presumably the presence of the tert-butyl group has added so much bulk to the system that it has become very sensitive to small changes in the reaction conditions, possibly resulting in the formation of a reagent with a completely different structure. In an attempt to determine the cause of the widely variable results when 88b was used several reductions of propiophenone were done under varying conditions. These are summarized in Table 6. It had been hoped that examination of some of the variables that have affected other systems would shed some light on the situation. Nos. 1-10 indicate that this approach failed for the most part. No conclusions can be drawn from these results because % ee values could not be consistently reproduced. Entry no. 2, for example, represents two duplicate experiments which gave widely different results even though an attempt was made to run the reductions under identical conditions.

The results listed in nos. 11-16 however do provide some insight as to the cause of the anomalous behavior. All of these reductions were carried out with standardized LAH solutions and all except no. 16 resulted in incomplete reduction and predominant formation of the S isomer in contrast to preferential R isomer formation when solid LAH was used in the conventional way so that a suspension results. This product configuration reversal is not an indication of a simple reagent solubility effect, however, since R alcohol was produced in no. 9 in which the initial LAH suspension was filtered before addition of the

Table 6. Reductions of propiophenone with LAH modified by 88b.^a



Reduction No.	Procedure Modification	% Reduction	Product % ee ^b (Configuration)
1	Ketone soln was added over 25 sec.	80 ^c	31 (<u>S</u>)
2	" " " " " 6 min.	100	82,50 ^d (<u>R</u>)
3	" " " " " 47 " .	90 ^e	23 (<u>S</u>)
4	A twofold amount of reagent was used.	100	44 (<u>R</u>)
5	The reagent was refluxed for 1/2 h then cooled to -78 ^o C over 25 min.	100	33 (<u>R</u>)
6	The reagent was formed at RT.	100	65 (<u>R</u>)
7	" " " " " -78 ^o C.	100	51 (<u>R</u>)
8	The modifier soln was added over 45 sec; the mixture was stirred for 15 sec then cooled to -78 ^o C over 8 min.	100	40 (<u>R</u>)

Table 6 continued.

<u>Reduction No.</u>	<u>Procedure Modification</u>	<u>% Reduction</u>	<u>Product % ee^b (Configuration)</u>
9	The LAH soln (mixture) was filtered.	100 ^f	15 (<u>R</u>)
10	The reaction was worked up after 6h.	35 ^e	10 (<u>S</u>)
11	Procedure F was used. ^g	82 ^f	23 (<u>S</u>)
12	" " " " . ^g	41 ^f	39 (<u>S</u>)
13	Procedure F was used and 1 equivalent of <u>i</u> -PrOH was added.	27 ^f	54 (<u>S</u>)
14	Procedure F was used and the hydrolysis was done with D ₂ O. ^g	95 ^f	43 (<u>S</u>)
15	Procedure F was used. ^g	70 ^f	35 (<u>S</u>)
16	" " " " . ^h	100 ^c	17 (<u>R</u>)

^aProcedure E was used in all reductions. See the experimental section for details.

^bSee footnote b in Table 4 for α_D lit. of PhCH(OH)Et.

Footnotes from Table 6 continued.

^c A very small amount of gas was evolved upon hydrolysis.

^d A repeat of the experiment.

^e Gas was evolved during the workup.

^f No gas evolution was observed during the workup.

^g The LAH solution was standardized by measuring the gas evolved upon hydrolysis of an aliquot with 2 N HCl. This method was subsequently found to be inaccurate. The amount of LAH present was therefore significantly less than theory.

^h The LAH solution was analyzed via the Stanford method which presumably provides an accurate analysis.

modifier. After experiments no. 11-15 had been completed it was reported to us in a private communication that researchers working with Professor H. S. Mosher at Stanford University had experienced difficulty with conventional methods of LAH analysis in connection with work on ketone reductions. Specifically it was found that analysis by measuring the gas evolved upon hydrolysis of aliquots of the solution gave hydride concentration results that did not accurately reflect the available reducing hydride content. Thus it became apparent that an insufficient amount of LAH had been used in experiments 11-15, but the exact amount used could not be determined. For no. 16 a more reliable method of LAH analysis for reducing hydride content developed at Stanford was used.¹⁰³ In this case there was complete reduction and the R isomer predominated. Since little gas was evolved upon hydrolysis of this reaction there must still remain some question as to the accuracy of the analysis, but there was more LAH present than in nos. 11-15.

It seems reasonable at this point to propose that a possible cause of the apparently random asymmetric induction is related to a variation in the amount of LAH present in solution. For example, with 87b, the dialkoxyaluminum hydride could produce R carbinol whereas a trialkoxy species could yield S carbinols. This rationalization of the unusual behavior of the 87b/LAH system however raises additional questions. How could the amount of LAH have varied in nos. 1-10? A coating of aluminum hydroxide or lithium aluminate can form on the surface of solid LAH. This coating causes LAH to decompose only slowly in moist air.¹⁰⁴ Such a coating would presumably also inhibit dissolution of the LAH in ether and reaction with the modifier. This argument is supported by the observation that the white precipitate that was separated from

the LAH solutions via filtration contained a significant amount of active hydride. This proposal is also supported by the fact that in those reactions where solid LAH had been used and where reduction was incomplete, gas was still evolved during the workup. The amount of LAH actually in solution could therefore depend on the extent of coating formation, particle size, and the rate of stirring. As a result, there may be a wide variation in the amount of available LAH in these reactions.

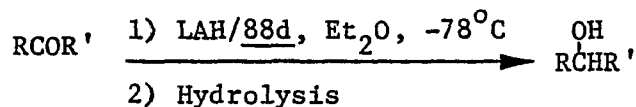
A question that remains is why there seemed to be insufficient hydride present in no. 16 (i.e., why was there little gas evolution during the workup) and why wasn't the % ee of the R isomer higher? There are at least two possible rationalizations. Perhaps some novel mechanism that causes destruction of 1 equivalent of hydride is occurring or maybe there is still a problem with the analysis of the LAH solution. Rather than attempt to speculate it would probably be better to subject the issue to further experimental tests. Discussion of this problem will be continued in conjunction with the following analysis of the results in Table 7. Although there are still problems with this system, 88b is potentially a modifier that can be used to produce either R or S carbinols of high optical purity.

Of all the modifiers tested, 88d provided the highest asymmetric induction most consistently. To determine the limitations of this ligand several different substrates were reduced. Table 7 summarizes these results. Unfortunately, this ligand appears to be really effective only in the reduction of acetophenone and propiophenone. Typically, increasing the size of the alkyl group of an alkyl phenyl ketone resulted in decreased asymmetric synthesis (no. 4). Also, not un-

commonly, pinacol was produced in low optical purity (no. 5).

The most intriguing results obtained with this ligand are those from the reduction of the acetylenic ketones. As was mentioned earlier, the formation of predominantly R carbinol in no. 6 is in agreement with the previously observed trend in the direction of asymmetric induction when acetylenic ketones are reduced (i.e., the acetylenic bond behaves as if it were similar sterically and/or electronically to the phenyl group in phenyl alkyl ketones). Therefore, in no. 6 the acetylenic group is acting as if it were the larger of the two groups attached to the carbonyl. But in no. 7 where an n-pentyl group has been added to the terminal acetylenic carbon, the alkyne function has taken the position of the smaller group resulting in a predominance of S alcohol. In no. 8, S alcohol is also preferentially formed although with the large iso-butyl group opposed to the alkynyl group. Perhaps it is not so surprising to see S alcohol predominate in this case. One rationalization is that possibly a mechanistic change has occurred. With the increase in steric bulk, a bimolecular rather than a unimolecular mechanism, like 90, may intervene. Change that is brought about by increased steric bulk of the substrate may also explain the predominant formation of (S)-pinacol.

No. 9, like no. 15 of Table 6, is a reduction in which there was an insufficient amount of hydride present due to the use of the conventional, but apparently unsuitable, gasometric procedure for LAH analysis. The amount of reduction that occurred in these two reactions was essentially the same. The amount of gas evolved during each stage of the two reactions was measured and it was found to be the same in both. The equality of the measured volumes and the identical reduction yields with the two ligands, 88b and 88d, suggest similar underlying behavior.

Table 7. Reductions with LAH modified by 88d.^a

Reduction No.	Ketone	% Reduction	Product % ee ^b (Configuration)
1	PhCOCH ₃	100	76, 81 (<u>R</u>)
2	PhCOEt	100	77, 68 (<u>R</u>)
3	"	59 ^c	34 (<u>R</u>)
4	PhCO <i>i</i> -Pr	61 ^d	27 (<u>R</u>) ^{e,f}
5	<i>t</i> -BuCOMe	96 ^d	5 (<u>S</u>) ^{e,g}
6	C ₅ H ₁₁ COC≡CH	100 ^h	20 (<u>R</u>)
7	C ₅ H ₁₁ COC≡CC ₅ H ₁₁	98 ^d	12 (<u>S</u>) ^e
8	<i>i</i> -BuCOC≡CCH ₃	96 ^d	5 (<u>S</u>) ^e
9	PhCOEt ^j	68 ^k	56 (<u>R</u>)
10	PhCOEt ^l	93 ^m	63 (<u>R</u>) ⁿ

^aProcedure E was used unless stated otherwise. See the experimental section for details.

^bThe % ee was calculated from the reported maximum rotation:

For α_D lit. of PhCH(OH)Me and PhCH(OH)Et see footnote b in Table 4; PhCH(OH)*i*-Pr, [α]_D²³ 48.3° (c 6.7, Et₂O)¹⁰⁰; *t*-BuCH(OH)Me, [α]_D²⁵ 8.10° (neat)¹⁰¹; for [α]_D of C₅H₁₁CH(OH)C≡CH see footnote in table 5; C₅H₁₁CH(OH)C≡CC₅H₁₁, [α]_D 2.93° (c 4.9, CHCl₃) for a sample of 62% ee (R)⁶⁹; *i*-BuCH(OH)C≡CCH₃, [α]_D²⁵ 13.5 (c 4.9, CHCl₃) for a sample of 93% ee (R)¹⁰².

^cGas was evolved during the workup.

Footnotes from Table 7 continued.

^dNo correction was made for the relative response ratio of the alcohol and the ketone.

^eThe ketone present in the product was treated simply as additional solvent.

^fAfter prep. GC to remove impurities, the product was still 28% ketone.

^gThe product contained a significant amount of ether but too little material was available for further purification. No correction was made for the ether that was present.

^hDetermined via IR.

ⁱThe product contained traces of impurities.

^jProcedure F was used. The LAH solution was analyzed by the gasimetric method; see footnote g in Table 6.

^kNo gas evolution was observed during the workup.

^lProcedure F was used. The LAH solution was analyzed by the Stanford method; see footnote h in Table 6.

^mA very small amount of gas was evolved during the workup.

ⁿAfter prep. GC to remove impurities, the product was still 2% ketone.

The significant difference is that only decreased asymmetric induction occurred in no. 9 as opposed to the reversal that was observed with 88b, in no. 15. It may be that, as suggested earlier, insufficient LAH results in the formation of a significant amount of a trialkoxyaluminum hydride species which, when 88d is the modifier, is simply a less effective asymmetric reducing agent than is the dialkoxy species.

In no. 10, which is like no. 16 of Table 6, the LAH solution was analyzed by the Stanford method to determine stoichiometry and there was a higher reduction and the formation of more of the R isomer. This further substantiates the argument that ratio of modifier to available LAH in solution is a crucial factor. The low % reduction and decreased optical yield in no. 3 may be explained on the same basis. There was little gas evolution, however, during the workup in no. 10 which again brings up the nagging question of the "missing" hydride.

The behavior of modifiers 88b and 88d appear to defy reasonable analysis. For example, in nos. 1, 2 and 3 of Table 6, measured aliquots of the same modifier and ketone solutions were used in the three different reactions and the ether for all three reactions came from the same graduated cylinder yet widely different results were obtained, apparently independent of the controlled variables. Also, the elemental analyses of the ligands are too close to theory for any appreciable amount of water or other reactive impurity to be present. No gas evolution was ever observed when the ketone solution was added to the reaction. All ligands could be recovered nearly quantitatively without loss of optical purity and in no. 14 of Table 6, no ^2H was incorporated into the recovered ligand or the carbinol product. All of this information suggests that the critical variable must be the amount of LAH present in the initial solution, or the form of the LAH species present (contact ion

pair, solvent separated ion pair, aggregate, etc). Perhaps the situation could be clarified by running a series of reductions using increasing amounts of a "standardized" LAH solution.

In an attempt to determine whether a group larger than methyl on the oxirane used to prepare the diol would result in a more effective modifier, n-butylamine was treated with 2 equivalents of (R)-(+) -styrene oxide. The initial product contained several impurities, presumably due at least in part, to attack of the amine at the 2^o carbon of the oxide. Despite these impurities, this crude material was tested as an LAH modifier. Using procedure A, propiophenone was reduced quantitatively in 14% ee to the S carbinol. When the temperature was lowered to -78^oC, 42% ee of the R carbinol was produced. Purification of the aminodiols mixture via column chromatography removed all but one major impurity. Reduction of propiophenone at -78^o (procedure E) using chromatographed material, resulted in 88% reduction to the S carbinol in 10% ee. The presence of the unknown impurity in the modifier renders any discussion of these results highly speculative. For this reason, and also because even the best result obtained with this system was not particularly impressive, no further work was done with it.

For comparison with the modified borate hydride results described earlier, (S,S,S)-TIPA was tested as an LAH modifier in the reduction of propiophenone. To insure that a substantial amount of reduction would occur, a twofold excess of hydride reagent was used. Procedure E was followed. There was 90% reduction and very little asymmetric induction (7% ee of the R isomer). Unlike the reagents formed from the aminodiols, this aminotriol produced an insoluble reagent.

Concluding Remarks

The work presented here leaves some unresolved problems in both the modified borohydride and the modified lithium aluminum hydride investigations. A foundation has been established, however, upon which future studies can be done with a reasonable expectation of success.

The chiral and achiral TIPAB hydride studies introduced a new chiral triol, borate and two new reducing agents, the kinetics and stereoselectivities of which are, at least, of academic interest. Modification of the symmetry of (S,S,S)-TIPAB may be accomplished in a variety of ways that could potentially result in a more effective asymmetric reducing agent. Some these modifications were discussed earlier. An approach which was not discussed is the preparation of boronic acid esters, in particular benzene boronates, PhB(OR)_2 , from the aminodiols and subsequent reaction with KH in THF to produce chiral benzene boronate hydrides, a type of hydride that has not yet been investigated.

In the course of the investigation of TIPABH, it was discovered that TIPAB and 2-octanol borate catalyze the reduction of phenyl t-butyl ketone by KH in THF. Although this may be of little synthetic value, it certainly has mechanistic implications which deserve further investigation. This observation does, of course, also introduce the phenomenon of catalytic hydride reductions using a hydride source such as KH.

Although the list of ideas that can be generated in connection with TIPA and TIPAB is extensive, only one more potential direction for future study will be mentioned. TIPA is soluble in both organic and

aqueous systems. As such, (S,S,S)-TIPA or derivatives of it could prove to be an effective chiral phase transfer catalyst.

The major problem that remains in the aminodiol-modified LAH system is the apparently inexplicable behavior of ligands 88b and 88d. Perhaps this situation can be clarified by further experimentation. It may be that consistent high asymmetric induction will be achieved via a systematic variation of the amount of LAH used. At present this work presents a new series of chiral aminodiolis which appear to be effective modifiers for LAH. Unfortunately, the extent of asymmetric induction observed in the reduction of acetylenic ketones was low. This appears to present the greatest challenge in future work with this system. It is clear that, in contrast to observations of previous studies^{56,69,70} the acetylenic group does not necessarily behave as if it were similar to a phenyl ring in such modified LAH reductions. Possibly modification of LAH by these aminodiolis results in a complex too rigid and sterically hindered to adopt a conformation that would interact in a sterically favorable manner with the acetylenic substrates to afford a high degree of asymmetric induction. The design of additional aminodiol ligands will have to consider this possibility. If this is true, simply increasing the bulk of the ligand will not necessarily result in a more effective modifier. However, by changing the size of the chelate ring (i.e., by putting the amine and alcohol functionalities in a 1,3- instead of a 1,2-position) and/or by careful modification of the groups on the non-carbinol and the carbinol arms of the modifier, a systematic study of the structural features of this system can be accomplished. By extending the present study in this manner it is not unreasonable to expect that a highly efficient modifier for acetylenic substrates will be found.

III. EXPERIMENTAL

General

Melting Points (mp)

All melting points were obtained using a Thomas-Hoover melting point apparatus and are uncorrected.

Infrared Spectra (IR)

IR spectra were recorded on a Perkin Elmer 283 B infrared spectrophotometer.

^1H Nuclear Magnetic Resonance Spectra (NMR)

NMR spectra were obtained on a Varian EM 360A NMR spectrometer. Chemical shifts are reported relative to tetramethylsilane. Splitting patterns are designated as: s, singlet; d, doublet; t, triplet; q, quartet; n, n peaks where n is any integer greater than 4.

^{13}C Nuclear Magnetic Resonance Spectra (^{13}C NMR)

^{13}C NMR spectra were obtained on a Jeol FX 90Q FT NMR spectrometer operated by Ms. K. Gallagher. Chemical shifts are reported relative to tetramethylsilane. The signal to noise ratio (S/N) is greater than 100/1 unless otherwise stated. Splitting patterns in the off resonance decoupled spectra are designated in the same manner as in the ^1H NMR spectra.

Optical Rotations

Optical rotations were determined on a Carl Zeiss Photoelectric Precision Polarimeter.

Elemental Analyses (CHN)

Elemental analyses were performed on a Perkin Elmer 240 B Elemental

Analyzer by Ms. D. Cardin.

Mass Spectra

Mass spectra were obtained on a Hitachi Perkin-Elmer RMU-6E mass spectrometer operated by Mr. W. Dotchin.

Gas Chromatography Analyses (GC)

GC were performed on a Varian Aerograph Model 90-P gas chromatograph coupled to a Sargent-Welch Model SRG recorder equipped with a Disc integrator. A 5% Zonyl E-7 on chromosorb G (80/100 mesh) column (11 ft. x 1/4 in.) was used in all analytical and preparative GC. Helium was used as the carrier gas at a flow rate of 50 ml/min. and the column temperature was 130°C unless otherwise stated.

Thin Layer Chromatography (TLC)

TLC for all carbinolamines was performed on basic alumina plates in 5% EtOH/CH₂Cl₂ unless otherwise stated.

Compounds

All compounds purchased from commercial sources were used as received unless otherwise noted.

Dry Solvents

Dry ether and THF were obtained by distillation from benzophenone ketyl under nitrogen and were used immediately.

Hydride Reductions

All glassware was oven-dried or flamed and cooled under nitrogen. All transfers in asymmetric reductions were done under nitrogen via stainless steel needle or syringe. Solid LAH was weighed out under nitrogen in a glove bag. KH/nujol was not handled under nitrogen except to initially break up the mass of settled KH.

Analysis of Butyl Lithium Solutions¹⁰⁵

All glassware was oven dried and n-butyl lithium transfers were

done under nitrogen.

A few crystals of 1,10-phenanthroline were placed in a round bottom flask which was then equipped with a magnetic stirring bar and a rubber septum cap. After flushing the flask with nitrogen, 1.00 ± 0.01 mL aliquots of the butyl lithium solution were successively added and titrated with a 0.999 M solution of s-butanol (distilled from CaH_2) in m-xylene (distilled from CaH_2) under nitrogen.

Gasometric Analysis of Lithium Aluminum Hydride Solutions

A $1.00 \pm .01$ mL aliquot of the ethereal LAH solution was injected into a sealed flask containing 2N H_2SO_4 /THF (1:1) and connected to a gas buret through dry ice/acetone trap. The buret was read and the volume of evolved gas was determined after all gas evolution had ceased and the volume of gas in the system appeared to have stabilized (usually after 1-2 min). This was repeated until 5 or 6 consecutive consistent volumes were obtained. To obtain the molarity of the hydride solution the average of these volumes was divided by four times the calculated volume of 1 mmol of gas.

Analysis of Lithium Aluminum Hydride Solutions by the Stanford Method¹⁰³

Acetophenone (0.7056 g, 5.88 mmol) and biphenyl (0.2060 g) were placed in an oven dried, 25 mL single-neck round bottom flask equipped with a magnetic stirring bar. The flask was sealed with a septum cap then flushed with nitrogen. Dry ether (3 mL) was added and the resulting solution was cooled in an ice bath. A $1.00 \pm .01$ mL aliquot of the ethereal LAH solution was added and the reaction was then stirred at 25-35°C for 2 h. H_2O (1 mL), saturated NH_4Cl solution (4 mL), and concentrated HCl (0.5 mL) were added and the mixture was stirred vigorously for a few minutes. The

two layers were allowed to separate overnight. The upper organic layer was analyzed by GC for alcohol and ketone content. The molarity of the hydride solution was calculated by subtracting the amount (mmol) of unreacted ketone from 5.88 then dividing by 4.

Percent Enantiomeric Excess (% ee)

The % ee of a product was determined by dividing the observed rotation by the literature value reported for optically pure material then multiplying by 100. In cases where propiophenone was incompletely reduced, the maximum rotation for the carbinol containing a known amount of ketone (determined via GC as described previously) was determined using the plot shown in figure 12.

Synthetic

Ethylene Oxide

NaH/nujol (50% suspension, 26.4 g, ca. 0.55 mol of KH) was placed in a round bottom flask equipped with an addition funnel, mechanical stirrer and a short path distillation head vented through a dry ice/acetone condenser. Bis(2-methoxyethyl) ether (100 mL), distilled from CaH_2 and stored over Na, was added quickly under nitrogen. A significant amount of gas was evolved. 2-Chloroethanol (33.5 mL, 40.25 g, 0.5 mol) was added dropwise to the stirred slurry of NaH/diglyme under nitrogen. After a small amount of the chlorohydrin had been added, the reaction mixture became quite warm and the product began to shoot out through the stillhead along with the H_2 that was

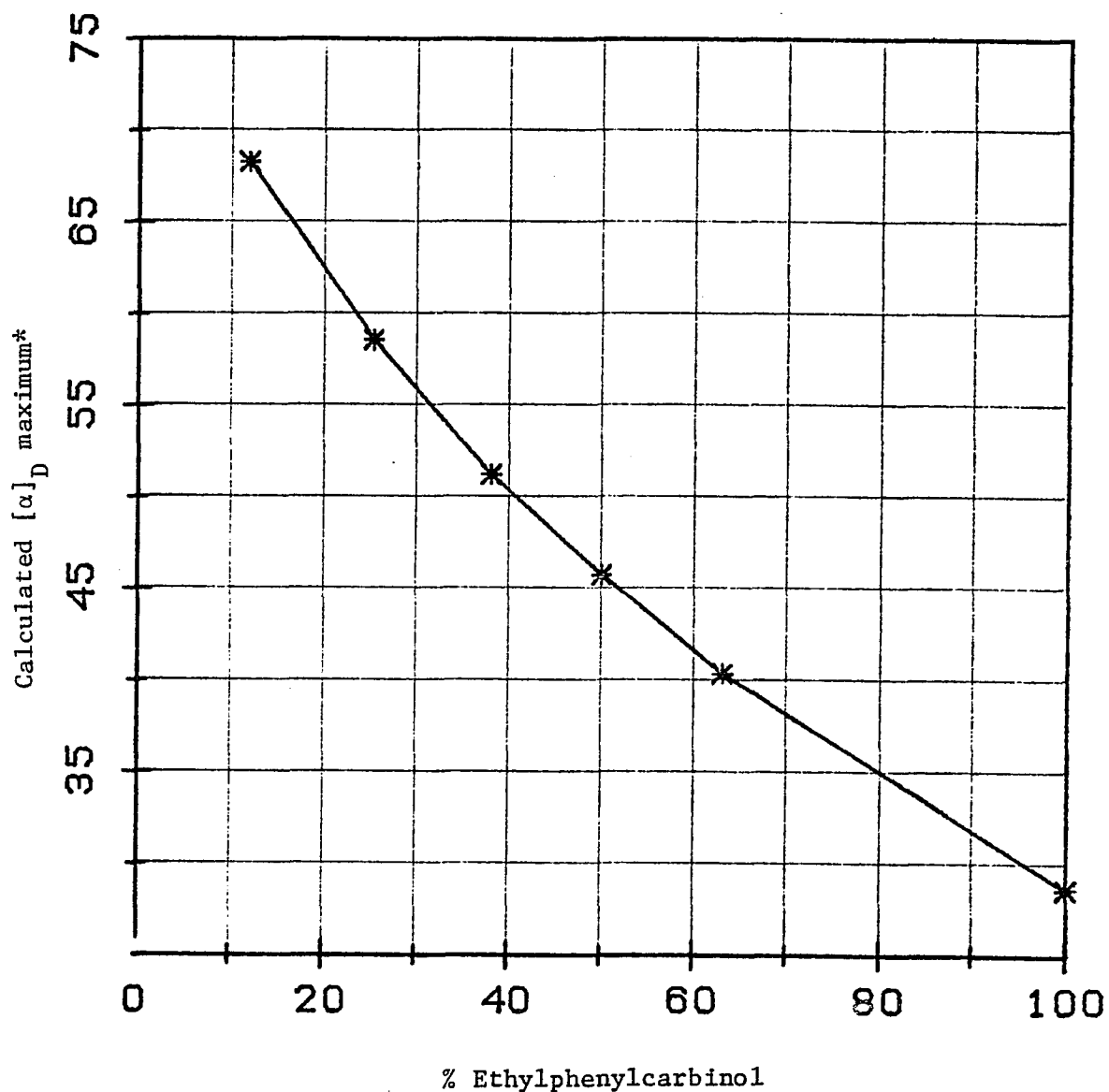


Figure 12. The apparent maximum rotation of PhCH(OH)Et in a mixture of PhCH(OH)Et and PhCOEt calculated by assuming that the ketone is an inert diluent.

*A sample of optically active ethylphenylcarbinol (36% ee of the R isomer) was obtained by an asymmetric reduction. Weighed amounts of alcohol and ketone were used to make solutions of known concentration. The rotation of the solutions was measured and the specific rotation was multiplied by 2.77 to give the plotted values.

produced. The rate of distillation was easily controlled by the rate of chlorohydrin addition. Any of the product that did not condense in the stillhead condenser was condensed on the dry ice/acetone condenser. The head temperature rose as high as 55°C (lit.¹⁰⁶ bp 13-14°C). Within 15 minutes all of the chlorohydrin had been added and the reaction had ended yielding 19.54 g (89%) of the oxide: NMR (CDCl₃) δ 2.70 (s, CH₂), 3.33 and 3.60 (small s, impurities - probably H₂O).

Ethyl (S)-2-(Tetrahydro-2-pyranoxy)propanoate (67)⁸⁹

Dihydropyran (456 mL, 420 g, 5.01 mol) in dry ether (600 mL) was added to ethyl (S)-(+)-lactate (342 mL, 354 g, 3 mol) in a water bath cooled round bottom flask. Toluenesulfonic acid (300 mg) was added and the reaction mixture was stirred for 10 h under nitrogen. Sodium carbonate (30 g, 282 mmol) was added and stirring was continued for 4.5 h. The solid material was separated via filtration and washed with a small amount of ether. The filtrate was concentrated (Rotavapor) then distilled through a 10" Vigreux column to afford 591.2 g (98%) of the THP protected ester: bp 83°C (0.75 mm)-66°C (0.22 mm), mostly 68-70°C (0.32 mm), [lit.⁸⁹ bp 65-69°C (0.25 mm)]; NMR (CDCl₃) δ 1.18-2.0 (m, 12H CH₂ and CH₃), 3.29-4.0 (m, 2H, CH₂O), 4.0-4.62 (9, 3H, CH and CH₂O₂C), 4.72 (Broad s, 1H, CHO₂).

(S)-2-(Tetrahydro-2-pyranoxy)-1-propanol (68)⁸⁹

A solution of ethyl(S)-2-(tetrahydro-2-pyranoxy) propanoate (190 g, 0.95 mol) in dry ether (250 mL) was added dropwise over 3 h, under nitrogen to a stirred, ice-water cooled slurry of LAH (20.9 g, 0.55 mol) in anhydrous ether (750 mL). The reaction mixture was then refluxed overnight (16 h). The ice-water cooled mixture was hydrolyzed by the sequential addition of H₂O (21 mL), 15% NaOH (21 mL) then H₂O (63 mL).

The solid material was separated via suction filtration then washed with ether. The combined filtrate and washings were dried (Na_2SO_4) and evaporated (Rotavapor) to give 134.3 g of a slightly yellow liquid. This was distilled through a short path distillation apparatus to yield 105.56 g (70%) of product: bp $90\text{--}95^\circ\text{C}$ (2.50 mm) (mostly $90\text{--}92^\circ\text{C}$) [lit.⁸⁹ bp $63\text{--}72^\circ\text{C}$ (1 mm); $\alpha_D^{22} 9.35^\circ$ (neat); NMR (CDCl_3) δ 1.14 and 1.23 (2d, 3H, CH_3), 1.33–2.06 (broad s, 6H, CH_2), 2.86–4.23 (m, 6H, CH_2O , CHO and OH), 4.5–4.9 (broad d, 1H, CHO_2).

(S)-1-(p-Toluenesulfonyl)-2-(tetrahydro-2-pyranyloxy)propane (69)⁸⁹

Toluenesulfonyl chloride (136 g, 0.712 mol) was added in portions over 45 min to an ice-water cooled, stirred solution of (S)-2-(tetrahydro-2-pyranyloxy)-1-propanol (103.5 g, 0.651 mol) in dry pyridine (160 mL). The formation of pyridine hydrochloride was evident within 15 minutes after the addition of the first portion. The mixture was allowed to stand in the refrigerator for approximately 31 h. The precipitated pyridine hydrochloride was filtered off and rinsed with benzene (160 mL) in 3 portions. The combined filtrate and washings were concentrated (Rotavapor, at 50°C), the residue was added to 400 mL of ice/ H_2O and the layers were separated. The organic layer was washed three times with 3N HCl (200 mL), two times with H_2O (200 mL) then dried (Na_2SO_4). Evaporation of the filtrate (Rotavapor, at 60°C) afforded 181 g (95%) of the tosylate: NMR (CDCl_3) δ 1.18 (broad m, 3H, CH_3), 2.55 (broad s, 6H, CH_2 of the THP moiety), 2.43 (s, 3H, $\text{CH}_3\text{-Ph}$), 3.18–4.36 (broad m, 5H, CH_2O and CHO), 4.65 (s, 1H, CHO_2), 7.16–8.06 (2d, 4H, Ph).

(S)-1-(p-Toluenesulfonyl)-2-propanol (70)⁸⁹

(S)-1-(p-Toluenesulfonyl)-2-(tetrahydro-2-pyranyloxy) propane (117 g, 0.4 mol), Dowex 50W-X8 (4 g, 20 meq H^+) and methanol (250 mL were

combined in an Erlenmeyer flask and stirred for 24 h. The Dowex-50 was separated via filtration and the filtrate was evaporated (Rotavapor, at 60°C) to give 94.40 g of material that was shown to be only 68% deprotected via NMR (using the integration of the THP CH₂ peak at δ 1.55 and the CH₃ peak at δ 1.13). The crude product was combined again with methanol (250 mL) and Dowex-50 (4 g) and stirred an additional 24 h. The ion exchange resin and solvent were removed as above to afford 84.3 g (101%) of product which was calculated to be 99% deprotected by yield and 90% deprotected via NMR as above: NMR (CDCl₃) δ 1.13 (d, 3H, CH₃), 2.43 (s, 3H, CH₃-Ph), 2.83 (s, 1H, OH), 3.58-4.29 (m, 3H, CH and CH₂), 7.16-7.98 (2d, 4H, Ph) also small peaks at δ 1.55 (s, CH₂ of THP), 3.40 (d) and 4.67 (s, CHO₂ of THP); lit.⁸⁹ mp 35-36°C.

(S)-2-Methyloxirane(71)-Method A⁸⁹

(S)-1-(p-Toluenesulfonyl)-2-propanol (75.59 g, 0.361 mol) was placed in a 500 mL, 3-neck, round bottom flask equipped with a magnetic stirring bar and a one piece distillation head (condenser water at 3-17°C) leading to a dry ice/acetone cooled receiver. KOH (112.7 g, 2.01 mol) and H₂O (42 mL) were added and the flask was stoppered. The reaction mixture turned to a sponge-like brown mass and the oxide began to come over almost immediately. When the evolution of oxide had ceased, H₂O (50 mL) was added, the resulting slurry was heated and the distillate was collected until the head temperature had reached 95°C. The crude product (15.47 g) was distilled over KOH through a 3" Vigreux column to give 12.89 g (62%) of (S)-Propylene oxide: bp 34-36°C [lit.⁸⁹ bp 34-35°C]; $[\alpha]_D^{25}$ -13.37° (neat) [lit.⁹⁴ $[\alpha]_D^{20}$ -14.65° (neat)] NMR (CDCl₃) δ 1.32 (d, 1H, CH₃), 2.43 (q, 1H) and 2.80 (t, 1H) diastereotopic ¹H's, 2.95 (m, 1H, CHO); GC 1 peak, ret. time 3.8 min (50°C,

75 mL/min).

(S)-(+)-Propylene Glycol (72)*

LAH (95%, 66 g, 1.65 mol), weighed out under nitrogen, was added in portions to stirred, cold (0-5°C), dry ether (1.8 L) under nitrogen. Another 100 mL of ether was added to wash down the LAH that had stuck to the wall of the flask. A solution of (S)-ethyl lactate (236 g, 2 mol) in dry ether (400 mL) was added dropwise over 5 h to the ice-water cooled slurry of LAH in ether. The mixture was then stirred approximately 21 h. The reaction mixture was cooled with an ice-water bath then acetone (60 mL) was added dropwise over 1.25 h. After stirring for an additional 0.5 h H₂O (66 mL) was added dropwise over 0.5 h. The mixture was stirred for 0.5 h then 15% NaOH (66 mL) was added dropwise over 10 min. After 5 min of additional stirring, H₂O (198 mL) was added dropwise over 45 min. The hydrolyzed mixture was stirred for approximately 1.5 days, i.e. until no gray material was left in the mixture. Acetone (1.2 L) was added and the mixture was stirred for 2 h then allowed to settle for several h. The solid material was separated via filtration, washed several times with acetone then put aside for further treatment. The combined filtrate and washing were concentrated (Rotavapor) to give a crude yield of 134.6 g which was distilled through a 10 cm Vigreux column to afford 111.01 g (73%) of the diol: bp 91°C (8.75 mm)-91°C (7.75 mm); α_D^{18} 17.1° (neat) [lit. bp¹⁰⁶ 101.8°C (24 mm), α_D^{25} 16.35° (neat)¹⁰⁸]; NMR (CDCl₃) δ 1.13 (d, 3H, CH₃), 3.16-3.63 and 3.63-4.10 (2m, 3H, CH and CH₂), 4.46 (s, 2H, OH).

*This is a modification of the procedure used by Mori to reduce (S)-(-)-leucic acid to the corresponding diol in 50% yield.¹⁰⁷

The solid material from above was made acidic with 2N H_2SO_4 , diluted with H_2O then extracted for several days with CH_2Cl_2 . The CH_2Cl_2 solution was concentrated (Rotavapor) to give a crude residue (20.70 g) which was distilled, bp $35\text{--}89^\circ\text{C}$ (6.05 mm), through a short path distillation apparatus to give 14.03 g of material which was determined to be something other than propylene glycol via NMR.

(S)-(-)-2-Acetoxy-1-bromopropane (73)⁹²

HBr/AcOH (834 mL, 4.32 mol) was added with stirring to ice-water cooled (S)-(+)-propane-1,2-diol (109.45 g, 1.44 mol) over approximately 1 h. The bath was removed and the reaction was stirred at room temperature for 2 h. H_2O (1.5 L) was added and the mixture was neutralized with Na_2CO_3 . H_2O (0.5 L) was added to dissolve the solid material present and the mixture was extracted 3 times with ether (750 mL). The organic extracts were combined, dried (Na_2SO_4) and concentrated (Rotavapor, less than 50°C) to give 278.7 g of dark liquid. This was distilled through a 6" Vigreux column to yield 215.83 g (83%) of the ester: bp 63°C (12.5 mm)– 70°C (9.25 mm) [lit.⁹² bp 57°C (11 mm)]; NMR (CDCl_3) δ 1.36 (d, 3H, CH_3), 2.07 (s, 3H, CH_3CO_2), 3.43 (d, 2H, CH_2), 5.06 (m, 1H, CH) and 4.26 (small m, due to trace of 1-acetoxy-2-bromo isomer).

Potassium Pentoxide

Potassium (ca. 60 g, 1.5 mol), rinsed then weighed out in pentane, was added in pieces to 1-pentanol (distilled from Na) under nitrogen. The mixture was stirred until the last traces of K had reacted. Aliquots (1 mL) were added to water then titrated with standardized HCl solution (0.2003 N) using phenolphthalein indicator. Approximately 1 L of 1.55 M solution was obtained.

(S)-(-)-1,2-Epoxypropane (71)-Method B⁹²

(S)-(-)-2-Acetoxy-1-bromopropane (9.05 g, 50 mmol) and 1-octanol* (20 mL) were placed in a 100 mL round bottom flask equipped with an addition funnel, mechanical stirrer and a micro short path distillation head attached to a 10" Vigreux column. The stillhead was vented through a dry ice/acetone condenser. A 1.55 M solution of potassium pentoxide in 1-pentanol (32.3 mL, 50 mmol) was added dropwise with stirring at room temperature. When the addition had been completed, the addition funnel was replaced with a thermometer and the stirred mixture was heated (oil bath) rapidly to 100°C. This was insufficient heat to drive the oxide through the Vigreux column so the temperature was increased slowly. Oxide began to come over when the pot temperature had reached 117°C. Increasing the temperature was continued in an attempt to keep the distillation rate high enough to maintain a head temperature of approximately 34°C. The distillation was extremely slow (1.5 h). Collection of the product was discontinued when the head temperature began to rise above 34°C (oil bath at 173°C and pot temp. at 149°C). to give 2.38 g (82%) of optically active oxide: bp 34-35°C [lit.⁸⁹ bp 34-35°C]; $[\alpha]_D^{21}$ -14.002° (neat) [lit.⁹⁴ $[\alpha]_D^{20}$ -14.65° (neat)]; NMR (CDCl₃) δ 1.30 (d, 3H, CH₃), 2.39 (q, 1H) and 2.70 (q, 1H) (CH₂), 2.97 (m, 1H, CHO); GC 1 peak, ret. time 1.3 min (130°C, 60 mL/min).

(R)-(-)-2-Brosyloxy-1-phenylethanol¹⁰⁹

To a stirred solution of p-bromobenzenesulfonyl chloride (83.2 g, 0.325 mol) in pyridine (250 mL) at -10°C under nitrogen, a solution of (R)-(-)-1-phenyl-1,2-ethanediol (45.0 g, 0.325 mol) in pyridine

*Octanol was used simply because insufficient pentanol was available.

(250 mL) was added dropwise at a rate sufficient to keep the temperature below 5°C. The mixture was placed in the refrigerator for ca. 2 days during which only a small amount of crystalline material had formed. The mixture was removed from the refrigerator and allowed to stand at room temperature for 2 h. It was then poured into ice (1200 g)/conc. HCl (200 mL) and the gummy product was taken up in ether by extracting 3 times with ca. 600 mL of ether. The ethereal solution was dried (Na_2SO_4) and concentrated (Rotavapor). An attempted recrystallization of the oily residue from 270 mL of benzene/light pet. ether (5:4 by vol) failed. The solvent was removed (Rotavapor) to yield 89.90 g (77%): NMR (CDCl_3) δ 3.0 (s, 1H, OH), 4.05 (d) and 4.26 (s) (2H, CH_2), 4.93 (2d, 1H, CH), 7.27, 7.32 and 7.62 (3s, 11H, Ph). Although the NMR spectrum indicates the presence of an impurity, this product was used without further purification.

(R)-(+)-Styrene Oxide¹⁰⁹

(R)-(-)-2-Brosyloxy-1-phenylethanol (89.90 g, 0.214 mol) was dissolved in ether (400 mL) then the solution was cooled to -15°C. A solution of KOH (16.0 g, 0.287 mol) in methanol (160 mL) was added dropwise at a rate sufficient to keep the temperature below 3°C. Shortly after the addition had been completed, H_2O (750 mL) was added and the voluminous white precipitate dissolved readily. The layers were separated and the aqueous layer was extracted with ether. The combined organic layers were dried (Na_2SO_4) then concentrated (Rotavapor) leaving 60.3 g of a yellow suspension. This was distilled to yield 20.36 g (68%) of the oxide: bp 60.5°C (1.70 mm)-63.5°C (2.0 mm) [lit.¹¹⁰ bp 90-92°C (20 mm)]; $[\alpha]_D^{22}$ 29.26° (neat) [lit.¹⁰⁹ $[\alpha]_D$ 34.2° (neat)]; NMR (CDCl_3) δ 2.73 (2d, 1H) and 3.10 (2d, 1H) (CH_2), 3.80 (2d, 1H, CH), 7.30 (s, 5H, Ph)

A second fraction was obtained: Yield, 5.21 g (17%); bp 54.5–60°C (0.85 mm); $[\alpha]_D^{23}$ 26.90° (neat); the NMR spectrum (CDCl_3) was identical to that of fraction 1.

(S)-2-(Tetrahydro-2-pyranoxy)propanamide (78)

Ethyl (S)-2-(tetrahydro-2-pyranoxy)propanoate (193 g, 0.96 mol) and aqueous ammonia 29.3%, 1.0 L, 15.5 mol) were placed in a round bottom flask containing a magnetic stirring bar and equipped with a dry ice/acetone condenser on top of a reflux condenser. After stirring for 5.5 h at room temperature, the mixture was refluxed for 2 h producing a clear solution. The dry ice/acetone condenser was refilled and the solution was heated (Variac setting at 40) overnight (9 h). A clear yellow-orange solution remained and there was no ammonia odor. Water was removed (Rotavapor) then toluene was added and solvent was vacuum evaporated once again to give 159.0 g (95%) of crude product: NMR (CDCl_3) δ 1.40 and 1.50 (2d, diastereotopic CH_3 's) and 1.67 (broad s, CH_2) (9H), 3.20–4.03 (broad m, 2.16 H, CH_2O), 4.23 (2q, 1H, CHO), 4.67 (broad s, 0.7H, CHO_2), 6.55, 5.88 and 7.03 (3 broads, 2.25H, NH_2), also 7.20 and 2.34 (2s, toluene). Since there was no indication of any H_2O in the product, it was used without further purification in subsequent LAH reduction. A small sample was distilled for characterization: bp 125–129°C (1 mm); $[\alpha]_D^{22}$ -27.5° (c 2.43, CH_2Cl_2); NMR (CDCl_3) δ 1.40 (2d) and 1.47 (d) (diastereotopic CH_3 's) and 1.67 (broad s, CH_2) (9H), 3.20–4.0 (broad m, 1.9H, CH_2O), 4.25 (q, 1.3 H, CHO), 4.69 (broad s, 0.8H, CHO_2) 6.20 and 6.72 (2 broad s, 2.7H, NH_2). Anal. Calcd for $\text{C}_8\text{H}_{15}\text{NO}_3$: C, 55.49; H, 8.67; N, 8.09. Found: C, 55.23; H, 8.92; N, 8.87.

(S)-2-(Tetrahydro-2-pyranoxy)-1-aminopropane (79)*

A solution of (S)-2-(tetrahydro-2-pyranoxy)propanamide (103.8 g, 0.60 mol) in dry ether (250 mL) was added dropwise over 2 h to an ice-water cooled suspension of LAH (45.6 g, 12.0 mol) in dry ether (750 mL) under an atmosphere of nitrogen. The cooling bath was removed and the mixture was refluxed for 53 h. The reaction mixture was cooled (ice-water) then decomposed by the sequential dropwise addition of H₂O (46 mL), 15% NaOH (46 mL) then H₂O (138 mL). The mixture was stirred for 2-3 h between each addition. The solid material was separated via suction filtration then washed several times with CH₂Cl₂. The combined filtrate and washings were concentrated (Rotavapor) approximately 6 weeks later to give 91.5 g of crude product which was distilled from KOH through a short path distillation apparatus to afford 42.8 g (45%) of the amine: bp 76°C (1.40 mm)-95°C (1.60 mm); α_D^{25} 14.05° (neat); NMR (CDCl₃) δ 1.17 (t, 3H, CH₃), 1.57 (s, 8H, CH₂ and NH₂), 2.70 (2d, 2H, CH₂N), 3.23-4.23 (m, 3H, CH₂O and CHO), 4.66 (s, 1H, CHO₂).

Bis[(S)-2-hydroxypropyl]-(S)-2-[tetrahydro-2-pyranoxy]-1-aminopropane (80)

(S)-(-)-Propylene oxide (3 mL, 0.158 mol) [α_D^{25} -13.37° (neat), was added dropwise under nitrogen to a stirred solution of (S)-2-(tetrahydro-2-pyranoxy)-1-aminopropane (3.98 g, 0.025 mol) α_D^{25} 14.05° (neat) and H₂O (6 mL) in a round bottom flask equipped with a reflux condenser. After stirring overnight (18.5 h) two layers had formed. The layers were separated and the organic layer was washed with saturated NaCl solution. The combined aqueous layers were extracted 3 times

*This is a modification of the procedure used to reduce the THP protected ethyl (S)-(+)-lactate.⁸⁹

with ether and the extracts and original organic layer were combined and concentrated (Rotavapor) to obtain a crude product (6.53 g 95%): NMR (CDCl_3) δ 1.10 (m, 9H, CH_3), 1.61 (s, 6H, CH_2 of THP), 1.95–2.88 (m, 6H, CH_2N), 3.25–4.23 (m, 7H, CHO, CH_2O and OH), 4.45 and 4.75 (2s, 2.2H, CHO_2). This product was used without further purification for the deprotection step.

Tris[(S)-2-hydroxypropyl]amine (81)-Method A

Concentrated HCl (3 mL, 34.8 mmol) was added to a nitrogen flushed flask containing a stirred solution of bis[(S)-2-hydroxypropyl]-(S)-2-[tetrahydro-2-pyranoxy]-1-aminopropane (6.53 g, 24 mmol) in methanol (30 mL). The solution was stirred for 21 h at which time KOH pellets (approximately 18) were added until the pH was approximately 10 (wet pH paper). Ether (30 mL) was added and the solid material was separated via suction filtration and washed with ether. The combined filtrate and washings were concentrated (Rotavapor) to give a residue (4.48 g) which crystallized upon standing. Distillation afforded 3.38 g (74%) of the optically active aminotriol: bp 118–142°C (1.15 mm) (mostly at 138–142°C); mp 88.5–97°C; $[\alpha]_D^{23}$ 196.08° (c 2.55, CH_2Cl_2); NMR (CDCl_3) δ 1.09 (d, 3H, CH_3), 2.0–2.65 (m, 2H, CH_2), 3.52–4.16 (m, 1H, CHO), 5.03 (s, 1H, OH). Anal. Calcd for $\text{C}_9\text{H}_{18}\text{NO}_3$: C, 56.54; H, 10.99; N, 7.33. Found C, 56.08; H, 11.33; N, 7.09 (10 months after preparation).

Tris[(S)-2-hydroxypropyl]amine (81)-Method B

(S)-(-)-Propylene oxide (21 mL, 0.30 mol) $[\alpha]_D^{26}$ -12.35° (neat), was added dropwise under nitrogen to a water bath cooled solution of aqueous NH_3 (29.6%, 6.4 mL, 0.10 mol) in H_2O (20 mL) in a flask equipped with a magnetic stirring bar and a dry ice/acetone reflux condenser. After stirring for 1 h the bath was removed, the condenser

was refilled and the reaction was left to stir over the weekend (64 h). The solution was concentrated, toluene was added and the solution was reconcentrated to give 16.02 g of crude product. This was distilled through a micro short path distillation apparatus to yield 14.76g (77%) of the optically active triisopropanolamine: bp 133-137°C (0.25 mm) (mostly 133-135°C); mp 89-99°C; $[\alpha]_D^{20}$ 191.337° (c 2.56; CH₂Cl₂); ¹H NMR (CDCl₃) δ 1.10 (d, 9H, CH₃), 1.97-2.07 (q, 6H, CH₂), 3.93 (m, 3H, CHO), 5.36 (s, 3H, OH); ¹³C NMR (CDCl₃) δ 19.83 (q), 63.66 (t), 63.93 (d), plus 6 small peaks indicating ca. 7.5% of what is probably an isomeric impurity; TLC R_f=0.29 and two barely visible spots at R_f=0.41 and 0.65. Anal. Calcd for C₉H₂₁NO₃: C, 56.54; H, 10.99; N, 7.33. Found: C, 56.18; H, 11.28; N, 7.18.

Triisopropanolamine Borate (TIPA) (64)⁸⁸

A solution of boric acid (29.7 g, 0.38 mol) and commercial triisopropanolamine (a racemic mixture of diastereomers) (92 g, 0.48 mol) in toluene (100 mL) was refluxed under nitrogen with continuous removal of water via a Dean-Stark trap until water formation ceased (26.5 mL of H₂O, 204% of theory was collected in ca. 4 h). The resulting clear solution was allowed to cool overnight. As much of the toluene as possible was decanted and the clean white crystalline residue was recrystallized from 400 mL of heptane/acetone (3:1 by vol). The recrystallized product was separated via suction filtration, washed with pentane then dried in vacuo over P₂O₅ to yield 64.0 g (67%) of the borate: mp 151-155°C (lit.⁸⁸ mp 154-157°C); NMR (CDCl₃) δ 1.0-1.50 (m, 3H, CH₃), 2.06-3.63 (2m, 2H, CH₂), 3.83-4.89 (m, 1H, CH).

Potassium Triisopropanolamine Borate Hydride (TIPABH) (65)*

KH/Nujol (24.7% suspension, total wt 6.48 g, ca. 40.0 mmol of KH) was weighed into an oven dried, 100 mL round bottom flask containing a magnetic stirring bar and equipped with a rubber septum cap. The flask was flushed with nitrogen and the Nujol was removed from the KH by washing 3 times with 30 mL of pentane. The pentane was transferred under nitrogen via stainless steel needle. When the last traces of pentane had been removed by blowing nitrogen through the flask, the flask was reweighed to verify the amount of KH (1.30 g, 32.5 mmol). Dry THF (10 mL) was added via stainless steel needle followed by a solution of triisopropanolamine borate (5.97 g, 30.0 mmol) in dry THF (50 mL). The mixture was stirred and analyzed periodically for hydride content by allowing the KH to settle, then injecting 1 mL aliquots of the supernatant liquid into 2 N HCl and measuring the volume of H₂ evolved. There appeared to be no significant hydride uptake within the first 27 h at room temperature after refluxing for 24 h, the cooled solution was found to be 0.547 M in hydride (ca. 100% of theoretical).

Tris[(S)-2-hydroxypropyl]amine Borate (85)

Tris[(S)-2-hydroxypropyl]amine (3 g, 15.7 mmol), boric acid (0.97 g, 15.7 mmol) and toluene (50 mL) were combined in a round bottom flask equipped with a magnetic stirring bar. The mixture turned to a clear solution upon heating. The solution was refluxed under nitrogen with continuous water removal via a Dean-Stark trap. After 3 h no more H₂O appeared to be coming off. After cooling, the resulting clear solution

*This is essentially the procedure used by Brown to form potassium triisopropoxyborohydride.^{86,87}

was concentrated (Rotavapor) and the residue was taken up in hot THF. Insoluble material was removed via filtration and washed with acetone. The solvent was removed from the combined filtrate and washings leaving a white solid (3.20 g). This was dissolved in boiling THF (ca. 5mL) and petroleum ether (110-115°C) was added to the clouding point (ca. 8 mL were required); crystals formed upon cooling to room temperature. The recrystallization mixture was placed in a refrigerator for a short time. The crystals were separated via suction filtration, washed with a small amount of pentane, then dried in vacuo to afford 2.50 g (80%) of product: mp 135-145°C; $[\alpha]_D^{24} 175^\circ$ (c 2.72, CH₂Cl₂) (A small amount of insoluble material was present in the rotation solution.); NMR (CDCl₃) δ 1.27 (d, 3H, CH₃), 2.42 (t, 1H, ¹H of CH₂ cis to CH₃), 3.23 (2d, 1H, ¹H of CH₂ trans to CH₃), 4.16 (m, 1H, CH). This material was subsequently found to be extremely hygroscopic (deliquescent).

Potassium Tris[(S)-2-hydroxypropyl]amine Borate Hydride (86)

KH/Nujol (24.7% suspension, total wt 3.05 g, ca. 18.8 mmol of KH) was weighed into a tared, oven-dried, round bottom flask equipped with a magnetic stirring bar and 2 septum caps. The flask was flushed with nitrogen and the Nujol was removed from the KH by washing it 3 times with 30 mL of pentane (dried over 3A molecular sieves). The pentane was transferred under nitrogen via stainless steel needle. When the last traces of pentane had been removed by blowing nitrogen through the flask, the flask was reweighed to double check the amount of KH (0.76 g, 19 mmol). One of the septa was replaced by an oven-dried reflux condenser, the flask was reflushed with nitrogen and dry THF (5 mL) was added. A solution of tris[(S)-2-hydroxypropyl]amine borate (2.44 g,

12.3 mmol) in dry THF (15 mL) was added via stainless steel needle followed by a 5 mL wash. The resulting mixture was stirred and refluxed under nitrogen for 24 h. Dry THF (10 mL) was added via syringe and refluxing was continued for an additional 0.5 h. After cooling and settling for 7 h, the clear solution was analyzed for hydride content by measuring the gas evolved when 1 mL aliquots were injected into 2N HCl. Based on the results of this analysis and solvent volume approximations, the solution was estimated to contain ca. 46% of the theoretical amount of hydride. The mixture was refluxed for an additional 24 h. At the end of this time the mixture had become noticeably darker, the septum had begun to deteriorate and there was noticeably less solvent present. The mixture was allowed to cool and settle for 5 h and was then analyzed again for hydride content as above. The solution was found to be 0.19 M in hydride.* The supernatant liquid (12 mL 2.28 mmol of hydride) was withdrawn via syringe and used directly in the reduction of propiophenone. The remaining KH was washed with dry THF (10 mL). The supernatant of this wash (6 mL) was also removed via syringe and added to the reduction of propiophenone.

Isopropyl Borate¹¹¹

Isopropanol (120 g, 2.0 mol), boric acid (31 g, 0.5 mol) and toluene (50 mL) were combined and refluxed under nitrogen in a 500 mL round bottom flask equipped with a Dean-Stark trap. Since water did not separate in the Dean-Stark trap, additional toluene (50 mL) and isopropanol (50 mL) were added. Refluxing was continued until 208 mL of the ternary azeotrope (toluene/iPrOH/H₂O = 49/38/13), theoretically

*Apparently impurities in the borate have caused the poor results of this reaction in comparison to the results obtained with the optically inactive borate.

containing 27 mL of H_2O , had been collected. The residue was distilled through a 6" Vigreux column and fraction that came off after the temperature had reached 134°C was collected to give 11.98g (13%) of product: bp $110\text{--}134^\circ\text{C}$ [lit.¹¹¹ bp $139\text{--}140^\circ\text{C}$]; NMR (CDCl_3) δ 1.12 (d, 6H, CH_3), 4.31 (m, 1H, CHO), 2.3 and 7.13 (2 small s, toluene), 1.23 (small s, presumably half of a doublet due to the CH_3 of iPrOH)

Potassium Triisopropoxyborohydride (KTPBH)^{86,87}

KTPBH was prepared via the same procedure as TIPABH from isopropyl borate (5.64 g, ca. 30 mmol), THF (60 ml) and KH/Nujol (24.7% suspension, total wt 6.48 g, ca. 40.0 mmol of KH) which actually contained 1.60 g of KH (40.0 mmol). Refluxing was unnecessary. The mixture was simply stirred for 6 h then allowed to settle for 15 h. The solution was found to be 0.323 M (ca. 65% of theory) in hydride.

N,N-Bis[(S)-2-hydroxypropyl]-1-aminobutane (87a)

(S)-(-)-Propylene oxide $[\alpha]_D^{25} -13.37^\circ$ (neat), (8 mL, 6.64 g, 114 mmol) was added to a stirred solution of *n*-butylamine (3.65 g, 50 mmol) in H_2O (12 mL) in a round bottom flask equipped with a reflux condenser. Within 10 min a tap water bath was required for approximately 10 min to control the exothermic reaction. Within 1 h after the oxide addition, two layers had formed. This mixture was stirred overnight (8 h), then concentrated (Rotavapor). Toluene was added and the solution was reconcentrated to give 9.70 g of crude product. This was distilled through a 1.5" Vigreux column to yield 6.17 g (65%)* of the aminodiol: bp $111\text{--}113^\circ\text{C}$ (1.35 mm); $\alpha_D^{22} 90.1^\circ$ (neat); $[\alpha]_D^{22} 137.37^\circ$ (c 3; CH_2Cl_2) (average rotation from 4 reactions, average deviation = 0.95° or 0.7%);

*A higher apparent yield (88%) can be obtained by collecting the product that begins to distill just 3 degrees lower than this cut. However, the product obtained when this lower boiling fraction is included has a second, small, faint spot in the TLC.

^1H NMR (CDCl_3) δ 0.70–1.68 (m, 13H, CH_2 and CH_3), 2.06–2.73 (m, 6H CH_2N), 3.43 (s, 2H, OH), 3.83 (6, 2H, CHO); ^{13}C NMR (CDCl_3) δ 14.03 (q), 20.32 (q), 20.53 (t), 29.19 (t), 55.15 (t), 62.63 (t), 63.98 (d); TLC one spot, $R_f=0.62$; mass spectrum, m/z (rel intensity) 189(4), 174(7) 144(100), 102(34), 70(28). Anal. Calcd for $\text{C}_{10}\text{H}_{23}\text{NO}_2$: C, 63.49; H, 12.17; N, 7.41. Found*: C, 63.26; H, 12.42; N, 7.34.

N,N-Bis[(S)-2-hydroxypropyl]-1,1-dimethyl-1-aminoethane (87b)

(S)-(-)-Propylene oxide, $[\alpha]_D^{22}-13.28^\circ$ (neat) (6.65 g, 115 mmol), tert-butylamine (3.65 g, 50 mmol) and H_2O (12 mL) were combined and stirred in a loosely-stoppered flask (which was stoppered more tightly after a few hours). Two layers did not form until the reaction had stirred for 25.5 h. The mixture was stirred for an additional 5 days then concentrated (Rotavapor). Toluene was added and the solution was reconcentrated to give 9.27 g of crude product. This was distilled through a 1.5" Vigreux column to afford 7.89 g (83%) of the aminodiol: bp 104°C (0.90 mm)– 106.5°C (0.95 mm); $[\alpha]_D^{20}108.43^\circ$ (c 2.8; CH_2Cl_2) (average rotation from 6 reactions, average deviation = 1.63° or 1.5%); ^1H NMR (CDCl_3) δ 1.09 (s) and 1.12 (s) (15H, CH_3), 2.03–2.8 (m, 4H CH_2N), 3.82 (s, OH) and 3.72 (m, CHO) (4H); ^{13}C NMR (CDCl_3) δ 20.54 (q), 27.22 (q), 55.08 (s), 58.94 (t) 66.09 (d); TLC $R_f=0.68$ and a second barely visible spot $R_f=0.04$ which did not disappear upon narrowing the bp range; Mass spectrum, m/z (rel intensity) 189(4), 174(6), 144(42), 88(100), 70(64). Anal. Calcd for $\text{C}_{10}\text{H}_{23}\text{NO}_2$: C, 63.49; H, 12.17; N, 7.41. Found*: C, 62.15; H, 12.62, N, 7.31.

*Consistent results could not be obtained, a problem that has been encountered by other workers⁷⁰ for similar compounds.

N,N-Bis[(S)-2-hydroxypropyl]-(S)-1-phenyl-1-aminoethane (87d)

(S)-(-)- α -methylbenzylamine $[\alpha]_D^{22} -37.9^\circ$ (neat), (12.10 g, 100 mmol), H₂O (24 mL) and (S)-(-)-propylene oxide, $[\alpha]_D^{22} -13.28^\circ$ (neat), (13.30 g, 230 mmol) were combined and stirred in a loosely stoppered round bottom flask. After several hours, the flask was stoppered more tightly and stirring was continued for 19 days. The mixture was concentrated (Rotavapor) and the crude product was distilled through a 1.5" Vigreux column to give 17.84 g (75%) of the aminodiol: bp 144-147°C (0.45 mm); $[\alpha]_D^{21} 158.208^\circ$ (c 3.4; CH₂Cl₂) (average rotation from 3 reactions, average deviation = 1.79° or 1.1%); ¹H NMR (CDCl₃) δ 1.05 (d, 6H, CH₃), 1.33 (d, 3H, CH₃), 2.00-2.72 (8, 4H, CH₂), 3.37 (s, 2H, OH), 3.80 (m, CHO) and 4.00 (q, CHPh) (3H), 7.40 (m, 5H, Ph); ¹³C NMR (CDCl₃) δ 11.76 (q), 20.37 (q), 57.97 (t), 58.56 (d), 64.52 (d), 126.99 (d), 127.80 (d), 128.23 (d), 143.18 (d); TLC one spot R_f=0.81; Mass spectrum, m/z (rel intensity) 237(8), 222(3), 192(92), 105(100), 88(84), 79(24), 77(28), 70(19). Anal. Calcd for C₁₄H₂₃NO₂: C, 70.89; H, 9.70; N, 5.91. Found*: C, 70.47; H, 10.10; N, 5.96.

N,N-Bis[(S)-2-hydroxypropyl]-(R)-1-phenyl-1-aminoethane (87c)

(R)-(+)- α -methylbenzylamine, $[\alpha]_D^{22} 39.4^\circ$ (neat), (6.05 g, 50 mmol), H₂O (12 mL) and (S)-(-)-propylene oxide, $[\alpha]_D^{22} -13.28^\circ$ (neat), (6.65 g, 115 mmol) were combined and stirred in a loosely stoppered, round bottom flask. After several hours the flask was stoppered more tightly and the reaction was stirred for 6 days. The mixture was concentrated and toluene was added. The solution was reconcentrated to give a crude product (11.93 g). This was distilled through a short path distillation

*See the footnote on page 100.

apparatus to give 9.0 g (76%) of product: bp 152-156°C (0.80 mm); TLC R_f =0.67 and another spot at R_f =0.42; ^{13}C NMR (CDCl_3) also indicated the presence of a significant impurity. The crude product was combined with a lower boiling fraction [bp 127-152°C (0.80 mm)] and was redistilled through a 6" Vigreux column to yield 7.32 g (62%) of the aminodiol: bp 154°C (1.10 mm)-157°C (1.0 mm); m.p.* 46-51°C; $[\alpha]_D^{20}$ 83.254° (c 3.2; CH_2Cl_2) (average rotation from 3 reactions, average deviation = 1.47° or 1.8%); ^1H NMR (CDCl_3) δ 1.07 (d, 6H, CH_3), 1.45 (d, 3H, CH_3), 2.36 (d, 4H, CH_2N), 3.49-4.22 (m, 5H, CH and OH), 7.31 (s, 5H, Ph); ^{13}C NMR (CDCl_3) δ 18.69 (q), 20.42 (q), 58.67 (t), 59.86 (d), 64.20 (d) 127.15 (d), 128.07 (d), 141.40 (d); TLC one spot R_f =0.61; mass spectrum, m/z (rel intensity) 237(8), 222(4), 192(87), 105(100), 88(89), 79(54), 77(58), 70(54). Anal. Calcd for $\text{C}_{14}\text{H}_{23}\text{NO}_2$: C, 70.89; H, 9.70; N, 5.91. Found**: C, 70.38; H, 10.01; N, 5.76.

N,N-Bis[2-hydroxyethyl]-(R)-1-phenyl-1-aminoethane (88)

(R)-(+)- α -methylbenzylamine (18.15 g, 0.15 mol) and H_2O (5 mL) were placed in a 3-neck round bottom flask equipped with a magnetic stirring bar, a dry ice/acetone reflux condenser and a cold (from a freezer) addition funnel. This mixture was cooled (ice-water) to 4-6°C. Ethylene oxide (15.18 g, 0.345 mol), weighed in a cold (freezer) graduated cylinder was added dropwise over 10 min during which time the reaction mixture became a clear solution. The reaction mixture was stirred for 1 h, and then the ice bath was removed and it was stirred

*This compound crystallized upon standing in a refrigerator for several months and after it had been used and recycled

**See the footnote on page 100.

for an additional 23 h. The reaction mixture was concentrated (Rotavapor), toluene was added to the residue, and the solution was reconcentrated to give 30.11 g of crude product. This was distilled through a short path distillation apparatus to give 20.50 g (65%) of product: bp 159°C (0.60 mm)-163°C (0.65 mm); TLC R_F =0.62, and a smaller, but significant, spot at R_F =0.66. This product was redistilled through a 6" Vigreux column to yield 17.16 g (57%) of the aminodiol: bp 160-163°C (1.2 mm); $[\alpha]_D^{20}$ -36.216° (c 2.90; CH_2Cl_2); ^1H NMR (CDCl_3) δ 1.41 (d, 3H, CH_3), 2.63 (2t, 4H, CH_2N), 3.16 (s, 2H, OH), 3.56 (t, 4H, CH_2O), 3.97 (q, 1H, CHN), 7.31 (s, 5H, Ph); ^{13}C NMR (CDCl_3) δ 15.44 (q), 52.17 (t), 59.32 (d), 60.19 (t), 126.99 (d), 127.85 (d), 128.18 (d), 142.70 (d); TLC R_F =0.51 and a barely visible spot at R_F =0.58; mass spectrum, m/z (rel intensity) 209(5), 194(5), 178(75), 105(100), 79(20), 77(25), 74(71). Anal. Calcd for $\text{C}_{12}\text{H}_{19}\text{NO}_2$: C, 68.90; H, 9.09; N, 6.70. Found*: C, 68.90; H, 9.55; N, 6.60.

N,N-Bis[(R)-2-hydroxy-2-phenylethyl]-1-aminobutane

n-Butylamine (4.38 g, 0.06 mol), H_2O (17 mL) and (R)-(+)-styrene oxide, $[\alpha]_D^{22}$ 29.26° (neat), (14.4 g, 0.12 mol) were added to a 100 mL round bottom flask equipped with a magnetic stirring bar and a reflux condenser. The flask was flushed with nitrogen and the reaction was stirred 17 h. The mixture was concentrated (Rotavapor), toluene was added and the solution was reconcentrated. The crude product was distilled through a micro short path distillation apparatus to yield 12.25 g of product: bp 220-225°C (0.95 mm); $[\alpha]_D^{24}$ -93.12° (c 1.89; CH_2Cl_2); ^1H NMR (CDCl_3) δ 0.90 (m, 3H, CH_3), 1.37 (m, 4H, CH_2), 2.32-

*See the footnote on page 100.

2.86 (d, 5.5H, CH_2N), 3.66 (s, 2H, OH), 4.7 (t, 1.8H, CHO), 7.30 (s, 10H, Ph) also 3.80 (small t, 0.65H, probably due to CHN resulting from amine attack at the 2° carbon of the oxide); TLC (silica gel/ Et_2O), $R_f=0.65$ plus 4 other smaller spots at $R_f=0$, 0.10, 0.21 and 0.76.

Due to the presence of impurities that apparently could not be removed via distillation, some (7.66 g) of the above product was chromatographed through silica gel (350 g) (column: 3.8 x 50 cm) with ether. 30 Fractions (ca. 20 mL each @ ca. 2mL/min) were collected. Fractions 17-28 were combined, filtered through a fine glass frit then concentrated (Rotavapor) to yield 7.35 g of material (96% recovery): $[\alpha]_D^{20} -87.5^\circ$ (c 2.4; CH_2Cl_2); ^1H NMR (CDCl_3) identical to that given above (further analysis of the integration indicated that the isomer resulting from amine attack at the 2° carbon of the oxide was present to the extent of ca. 8.4% of the product); ^{13}C NMR (CDCl_3) δ 14.03 (q), 20.48 (t), 28.98 (t), 54.93 (t), 62.95 (t), 70.75 (d), 125.90, 127.42, 129.29, 142.48 and 13 more small peaks verifying the presence of the previously mentioned isomer; TLC (silica gel/ Et_2O) one spot at $R_f=0.49$. Anal. Calcd for $\text{C}_{20}\text{H}_{27}\text{NO}_2$: C, 76.68; H, 8.63; N, 4.47. Found*: C, 77.21; H, 8.72; N, 4.85.

Recovery of Used Ligands

The standard procedure used to recover used ligands is exemplified in the following recovery of the tert-butylaminodiol.

The aqueous layers from several reactions were made basic with 15% NaOH (or KOH pellets) then extracted overnight with ether. Concentration of the solution in the collection flask afforded a pale yellow oil. This was distilled through a 1.5" Vigreux column to yield

*See the footnote on page 100.

14.96 g of the aminodiol which had characteristics identical to those of the newly prepared ligand. This accounted for 82% of all the tert-butylaminodiol that had been used. There was no indication of racemization in any of the recovered carbinolamines.

6-Tridecyne-8-ol

n-Butyl lithium in hexane (1.55 M, 193.5 mL, 0.30 mol) was added dropwise under nitrogen to a solution of freshly distilled heptyne (28.7 g, 0.30 mol) in THF (510 mL), distilled from benzophenone ketyl, at room temperature. Gas was evolved, the temperature rose slightly and a clear yellow solution was produced. This solution was stirred briefly until all gas evolution appeared to have ceased and was then cooled with a dry ice/acetone bath. A solution of freshly distilled hexanal (30.0 g, 0.30 mol) in THF (90 mL) was added dropwise. When the addition had been completed, the yellow color had disappeared. The cooling bath was removed and the reaction was stirred for 1 h. H₂O (ca. 50 mL) was added, the layers were separated and the organic layer was washed 3 times with H₂O then dried (Na₂SO₄) and concentrated (Rotavapor) to give 60.0 g of material. This residue was distilled through a 4" Vigreux column to yield 48.70 g (83%) of the acetylenic alcohol: bp 103-105°C (0.60 mm); IR (neat) 3320 cm⁻¹ (OH), 2220 (weak, C≡C); NMR (CDCl₃) δ 0.91 (t, 6H, CH₃), 1.06-1.90 (m, 4H, CH₂), 2.20 (m, 2H, CH₂C≡C), 2.73 (s, 1H, OH), 4.40 (broad t, 1H, CHO); ¹³C NMR (CDCl₃) δ 14.03 (q), 18.80, 22.32, 22.70, 25.08, 28.55, 31.20, 31.69 and 38.30 (t), 62.68 (d), 81.75 (s), 85.22 (s).

Propyne¹¹²

Dry (over Na) bis(2-methoxyethyl) ether (200 mL) was placed in a 3-neck round bottom flask equipped with a mechanical stirrer and a

rubber septum cap. The flask was flushed with nitrogen then cooled (dry ice/ CCl_4). LAH (19.0 g, 0.5 mol) was added in portions with stirring. When the LAH addition had been nearly completed, the reaction mixture suddenly solidified and stopped the mechanical stirrer. An additional 150 mL of diglyme were added slowly and the solid was broken up by manually operating the stirrer. The slurry was briefly stirred to further break up the lumps of LAH. A double-ended stainless steel needle was inserted through the septum. The other end was inserted into a dry ice/acetone cooled graduated collection tube that had been vented through a nitrogen bubbler. Propargyl bromide (20% in toluene, 74.4 g, 0.5 mol) in dry diglyme (75 mL) was added dropwise. Cooling was still necessary due to the amount of heat that was evolved. As this addition proceeded, the LAH broke up until it was a finely divided suspension. When the addition had been completed, the mixture was heated slowly for ca. 4-5 h until the amount of gas evolution was negligible and a total of 21 mL (74%) of propyne had been collected. The cooled (dry ice/ CCl_4) reaction mixture was hydrolyzed by adding H_2O (19 mL) dropwise. After stirring overnight, 15% NaOH (19 mL) then H_2O (57 mL) were added. The reaction mixture was still grey after all gas evolution had ceased. Upon heating it turned white and was disposed of.

6-Methyl-2-heptyn-4-ol

Propyne (21 mL, ca. 0.37 mol) was allowed to distil (bubble) into a hexane solution of *n*-butyl lithium (1.6 M, 156 mL, 0.25 mol) at room temperature under nitrogen. The reaction solution immediately became yellow and warm and a precipitate began to form. THF (250 mL), distilled from benzophenone ketyl, was added slowly as the propyne was being added. The reaction mixture turned brown. A water bath was added at this time. The color had lightened considerably by the time all

the THF had been added although the precipitate never dissolved. All of the propyne was bubbled into the mixture, but no gas (i.e propyne or butane) was evolved. THF (400 mL) was added but the precipitate still did not dissolve. A solution of freshly distilled isovaleraldehyde (21.5 g, 0.25 mol) in THF (ca. 90 mL) was added dropwise. The yellow color disappeared but returned whenever the rate of addition was very slow. Addition was stopped when ca. 1/3 of the aldehyde solution had been added and the reaction mixture was refluxed briefly. Gas was evolved; a deep yellow color appeared, but the precipitate did not dissolve. The reaction mixture was cooled with a water bath and addition of the aldehyde solution was continued. When all of the aldehyde solution had been added, the resulting clear brown solution was stirred for 1 h more. H₂O (ca. 50 mL) was added dropwise, the mixture was stirred briefly then extracted 4 times with H₂O (250 mL). The organic layer was dried (Na₂SO₄) and concentrated (Rotavapor) to give 28.2 g of crude product. This was distilled through a 1.5" Vigreux column to afford 22.16 g (70%) of the acetylenic alcohol: bp 75.5-80.5°C (7.20 mm) [lit.¹⁰² bp 60°C (3 mm)]; IR (neat) 3340 cm⁻¹ (OH), 2230 (weak, C≡C); ¹H NMR (CDCl₃) δ 0.93 (d, 6H, CH₃), 1.54 (m, CH₂ and CH) and 1.86 (s, CH₃C-C) (6H), 2.52 (s, 1H, OH), 4.40 (t, 1H, CHO); ¹³C NMR (CDCl₃) δ 3.47 (q), 22.59 (q), 24.87 (d), 47.29 (t), 61.16 (d), 80.61 (s), 80.99 (s).

Tert-butyl Phenyl Ketone¹⁰⁹

A solution of tert-butyl chloride (185.2 g, 2 mol) in dry ether (300 mL) was added over 2 h to an ice-water cooled mixture of Mg (48.6 g, 2 mol) in dry ether (500 mL). The reaction mixture was then stirred an additional 7.5 h under nitrogen. After the solid material had

settled to the bottom of the flask, the solution was added in portions over 0.5 h via stainless steel needle through a fritted glass filter to a mixture of benzonitrile (103 g, 1 mol) and CuCl (2.5 g, 25 mmol) in dry ether (250 mL). The solid residue from the Grignard reagent was washed with dry ether (500 mL) and the wash was added to the reaction mixture in the same manner as above. The mixture was refluxed under nitrogen for 2 h. 3 N HCl (1 L) was added and the mixture was refluxed for an additional 1.5 h. The aqueous and organic layers were separated and the aqueous layer was extracted 3 times with 250 mL of ether. The organic layer and washings were combined and washed 3 times with H₂O (250 mL) then dried (Na₂SO₄). Evaporation of the solvent (Rotavapor) afforded 154.2 g of pale yellow liquid which was distilled through a 10" column packed with copper mesh to give 124.85 g (77%) of the ketone: bp 48–55°C (0.32 mm) [lit.¹⁰⁹ bp 51–56°C (0.4 mm)] NMR (CDCl₃) δ 1.33 (s, 9H, CH₃), 7.23–7.75 (2m, 5H, Ph); GC indicated the presence of a trace of benzonitrile.

6-Methyl-2-heptyn-4-one-The Preparation of Acetylenic Ketones

Acetylenic ketones were prepared via the Jones oxidation¹¹³ of the corresponding alcohols. The method is typified by the preparation of 6-methyl-2-heptyn-4-one which follows:

A solution of CrO₃ (13.05 g, 0.1305 mol) and concentrated H₂SO₄ (11 mL) in H₂O (38 mL) was added dropwise under nitrogen over 2 h to a cooled (5–10°C), stirred solution of 6-methyl-2-heptyn-4-ol (19.06 g, 0.151 mol) in acetone (38 mL). When the addition had been completed, the mixture was stirred for an additional hour*, diluted with H₂O

*More time is required with some substrates. Stirring should be continued until all traces of red Cr(VI) have disappeared.

(240 mL) then extracted 3 times with ether (100 mL). The combined extracts were washed 2 times with saturated NaHCO_3 solution (60 mL) and once with H_2O (60 mL), then dried (Na_2SO_4) and concentrated (Rotavapor) to give 15.96 g of crude product which was determined to contain no alcohol** via NMR. This was distilled through a 1.5" Vigreux column to yield 13.21 g (71%) of the acetylenic ketone: bp $65-69^\circ\text{C}$ (6.5 mm); IR (neat) 2220 cm^{-1} ($\text{C}\equiv\text{C}$), 1673 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR (CDCl_3) δ 0.96 (d, 6.25 H, CH_3), 2.05 (s, 3H, $\text{CH}_3\text{C}\equiv\text{C}$), 2.36 (m, 2.72H, CH and CH_2) (The integration was difficult to determine accurately.) ^{13}C NMR (CDCl_3) δ 22.43 (q), 25.14 (d), 54.45 (t), 80.61 (s), 89.60 (q), 187.82 (s).

1-Octyn-3-one

This ketone prepared via the Jones oxidation¹¹³ of 1-octyn-3-ol (16.76 g, 0.133 mol) as described previously: Yield, 10.56 g, 64%; bp $59.5-61.5^\circ\text{C}$ (7.0 mm) [lit.¹¹⁴ bp $92-95^\circ\text{C}$ (46 mm)]; IR (neat) 3250 cm^{-1} ($\text{H}-\text{C}-\text{C}$), 2090 cm^{-1} ($\text{C}\equiv\text{C}$), 1675 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR (CDCl_3) δ 0.68-2.03 (m, 9H, CH_2 , and CH_3), 2.57 (t, 2H, CH_2CO), 3.30 (s, 1H, $\text{HC}\equiv\text{C}$); ^{13}C NMR (CDCl_3) δ 13.81 (q), 22.37 (t), 23.51 (t), 31.10 (t), 45.45 (t), 78.44 (d), 81.53 (d), 187.40 (s).

6-Tridecyn-8-one

This ketone was prepared via the Jones oxidation¹¹³ of 6-tridecyn-8-ol (25 g, 0.128 mol) as described previously: Yield 14.39 g (57%); bp $104-109^\circ\text{C}$ (1.90 mm); IR (neat) 2215 cm^{-1} ($\text{C}\equiv\text{C}$), 1675 cm^{-1} ($\text{C}=\text{O}$); ^1H NMR (CDCl_3) δ 0.91 (t, CH_3) and 1.41 (broad m, CH_2) (18H); 2.32 and 2.52 (2t, 4H CH_2CO and $\text{CH}_2\text{C}\equiv\text{C}$); ^{13}C NMR (CDCl_3) δ 13.92 (q), 18.96 (t),

**If the oxidation has been incomplete, the crude product may be re-oxidized. The appropriate amount of oxidizing agent can be calculated from the amount of alcohol present as determined via the NMR.

22.21 (t), 22.54 (t), 24.00 (t), 27.63 (t), 31.15 (t), 31.31 (t),
45.61 (t) 81.05 (s), 93.94 (s), 188.15 (s).

Hydride Reductions

Reduction of 2-Methylcyclohexanone with TIPABH

A solution of 2-methylcyclohexanone (1.12 g, 10 mmol) in dry THF (20 mL) was added under nitrogen to a THF solution of TIPABH (15 mL, 8.2 mmol) in an oven-dried 125 mL Erlenmeyer flask equipped with a magnetic stirring bar and a septum cap. The resulting solution was stirred for 18 h. Hydrochloric acid (40 mL of 1 M solution) was added and the mixture was stirred for ca. 5 min. Ether (30 mL) was added and the layers were separated. The aqueous layer was extracted 3 times with ether (20 mL) and the combined organic layers were washed 3 times with H₂O (50 mL), dried (Na₂SO₄) and concentrated (Rotavapor) to give 0.81 g of crude product. This was distilled through a micro short path distillation apparatus to yield 0.45 g of material: bp 30°C (0.10 mm); GC indicated 89% alcohol containing 72% of the cis isomer.

Reduction of 2-Methylcyclohexanone with KTPBH

The procedure was identical to that used to reduce the same substrate with TIPABH except as follows: 31 mL (10 mmol) of the KTPBH solution were used and the reaction was allowed to go for only 12 h. Hydrochloric acid (5%) was added until the pH of the reaction mixture was ca. 2 (wet pH paper). The layers were separated and the aqueous layer was extracted 2 times with 20 mL of ether. The organic layers were combined, washed 2 times with 20 mL of H₂O then dried (Na₂SO₄) and concentrated (Rotavapor) to give 1.15 g of residue. Distillation afforded 0.55 g of material: bp 32-35°C (0.15 mm); GC indicated 93%

alcohol containing 89% of the cis isomer.

Reduction of Propiophenone with (S,S,S)-TIPABH

An (S,S,S)-TIPAB hydride solution (12 mL, 2.28 mmol) and a THF wash (6 mL) of the flask containing it (see the previous preparation of the hydride soln) were added via syringe to an oven-dried, round bottom flask flushed with nitrogen and equipped with a magnetic stirrer and a septum cap. A solution of propiophenone (0.67 g, 5 mmol) in dry THF (5 mL) was added via stainless steel needle (followed by a 5 mL THF wash). The resulting solution was stirred at room temperature for 24 h. Hydrochloric acid (40 mL of 1 M solution) was added and the mixture was stirred for ca. 5 min. Ether (30 mL) was added and the layers were separated. The aqueous layer was extracted 3 times with ether (20 mL) and the combined organic layers were washed 3 times with H₂O (50 mL) dried (Na₂SO₄) and concentrated to give 0.70 g of material. GC showed 38% alcohol: (83% of theoretical based on hydride used) and traces of volatile impurities; NMR (CDCl₃) showed ca. 33-44% alcohol and no impurities other than ketone. Since small amounts of solid impurities appeared to be present, the crude product and the NMR sample were combined, taken up in ether, and filtered through a glass wool pipet plug. Concentration (Rotavapor) afforded 0.58 g (85%) of product: GC showed 37% alcohol with a trace of ether; $[\alpha]_D^{24} 7.01^\circ$ (c 38.5; PhCOEt), 14% ee based on $[\alpha]_D^{\max} 51.22^\circ$ from figure 12.

Reduction of Ketones with Aminodiol Modified LAH

Procedure A

The reduction of propiophenone is exemplary.

Dry ether (100 mL) was placed in a 250 mL, 3-neck, round bottom flask, flushed with nitrogen and equipped with a magnetic stirring bar

reflux condenser and an addition funnel. LAH (0.24 g, 6.0 mmol) was added followed by an additional 50 mL of dry ether to wash the last traces of LAH into the flask. The resulting suspension was stirred until a fairly clear grey solution was obtained (approximately 0.5 h). A solution of the aminodiol (6.4 mmol) in dry ether (25 mL) was added dropwise over 2-5 min. There was an immediate evolution of gas. The solution was stirred for 2-5 min before a solution of propiophenone (0.67 g, 5 mmol) in dry ether (25 mL) was added dropwise over 2-5 min. After stirring for 20 h the reaction mixture was hydrolyzed by the dropwise addition of 25 mL of H₂O (concomitant gas evolution). The organic layer was washed 3 times with 1 N HCl (25 mL), once with H₂O (25 mL), dried (Na₂SO₄) and concentrated (Rotavapor). The residue was distilled through a micro short path distillation apparatus to yield 0.57 g of crude product. This was analyzed via GC for % reduction prior to the measurement of the optical rotation.

Procedure B (Mosher's Procedure^{65,66})

This was identical to procedure A except for the following:

The total volume of ether used was only 48 mL distributed as follows: LAH was added to 20 mL of ether and washed down with an additional 5 mL. The aminodiol was dissolved in 20 mL of ether and added to the LAH suspension over 2 min. The mixture was stirred for 2-3 min and the ketone, in 3 mL of ether, was added dropwise via syringe.

The ethereal LAH was cooled to 0-5°C before addition of the aminodiol solution and this temperature was maintained for the first 15 h of the reaction. The reaction was then allowed to warm to room temperature for the remaining 5 h of the reduction.

Procedure C (Brinkmeyer's Procedure ⁶⁹)

This was identical to procedure A except for the following:

The temperature of the reaction was lowered to 0-5°C prior to the addition of the aminodiols solution. After adding the modifier solution over 2 min and stirring for 2-3 min as in procedure A, the temperature was lowered to -78°C over 10 min then the ketone solution was added slowly over ca. 0.5 h. The low temperature was maintained for ca. 7.5 h at which time the mixture was allowed to warm to room temperature for the remainder of the reaction.

Procedure D (Cohen's Procedure ⁷⁰)

This was identical to procedure A except for the following:

The ethereal LAH was cooled to 0-5°C prior to addition of the aminodiols solution. After addition of the modifier solution over 2 min and stirring for an additional 2-3 min, the temperature of the reaction was lowered to -78°C over 10 min and the ketone solution was added over 5-10 min. This temperature was maintained for ca. 9.5 h.

Procedure E (Standard Procedure)

This is the standard procedure that was used in most of the reductions. It is identical to procedure D (Cohen's procedure) except that the ketone was added over only 2 min and the -78°C temperature was maintained only for as long as the dry ice/acetone bath lasted (ca. 7 h).

Procedure F

This is identical to procedure E except that a standardized¹⁰³ ethereal solution of LAH was used and sufficient dry ether was added to bring the volume of the LAH/ether to 150 mL as in procedure A.

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